Neurology

OFFICIAL JOURNAL OF
THE AMERICAN ACADEMY OF NEUROLOGY

MAY—1959

Volume 9 - Number 5

the tranquility of freedom

For the epileptic, what satisfaction can transcend the simple freedom to come and go . . . without fear. This precious gift of a normal life can be yours to give today, thanks in part to a finer knowledge of the disease—and improved drug therapy. Five anticonvulsants that have contributed much to the control of epilepsy are presented here. Won't you send for our detailed literature?

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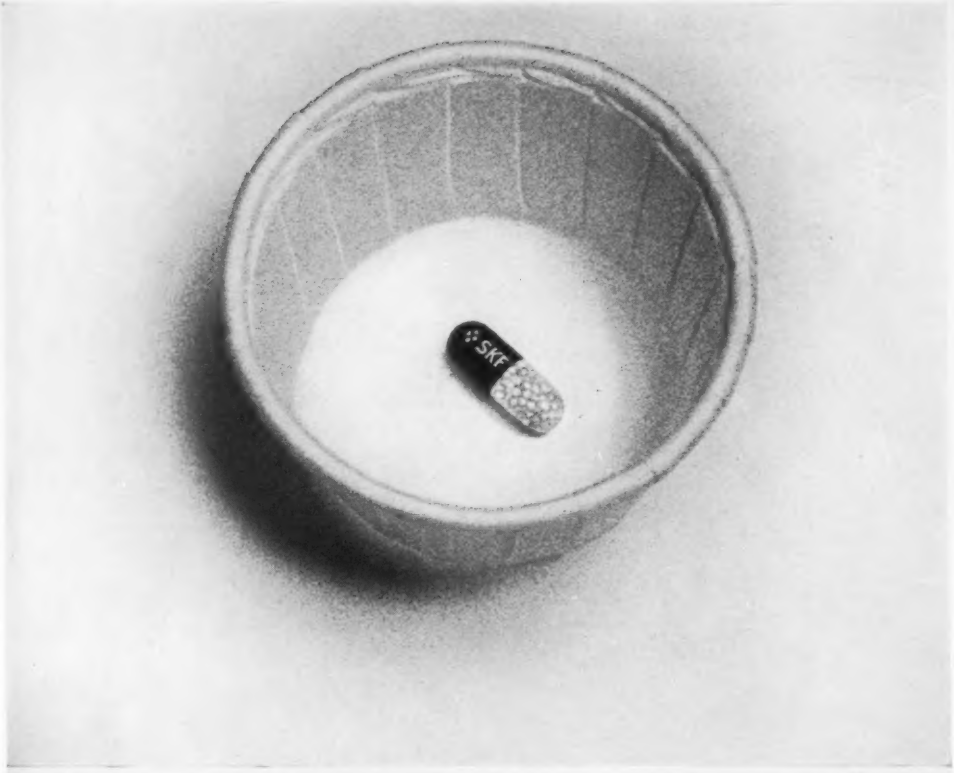

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NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.

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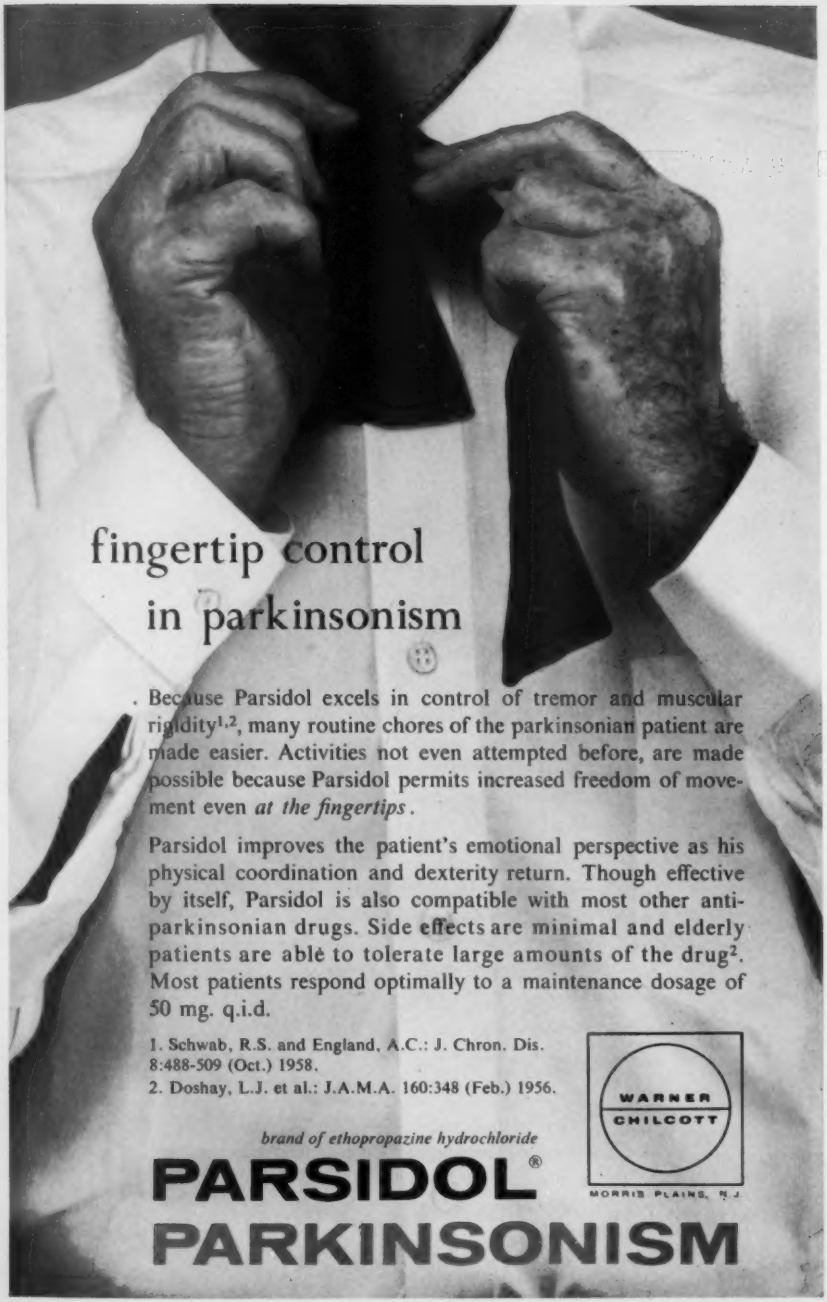
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2. Doshay, L.J. et al.: J.A.M.A. 160:348 (Feb.) 1956.
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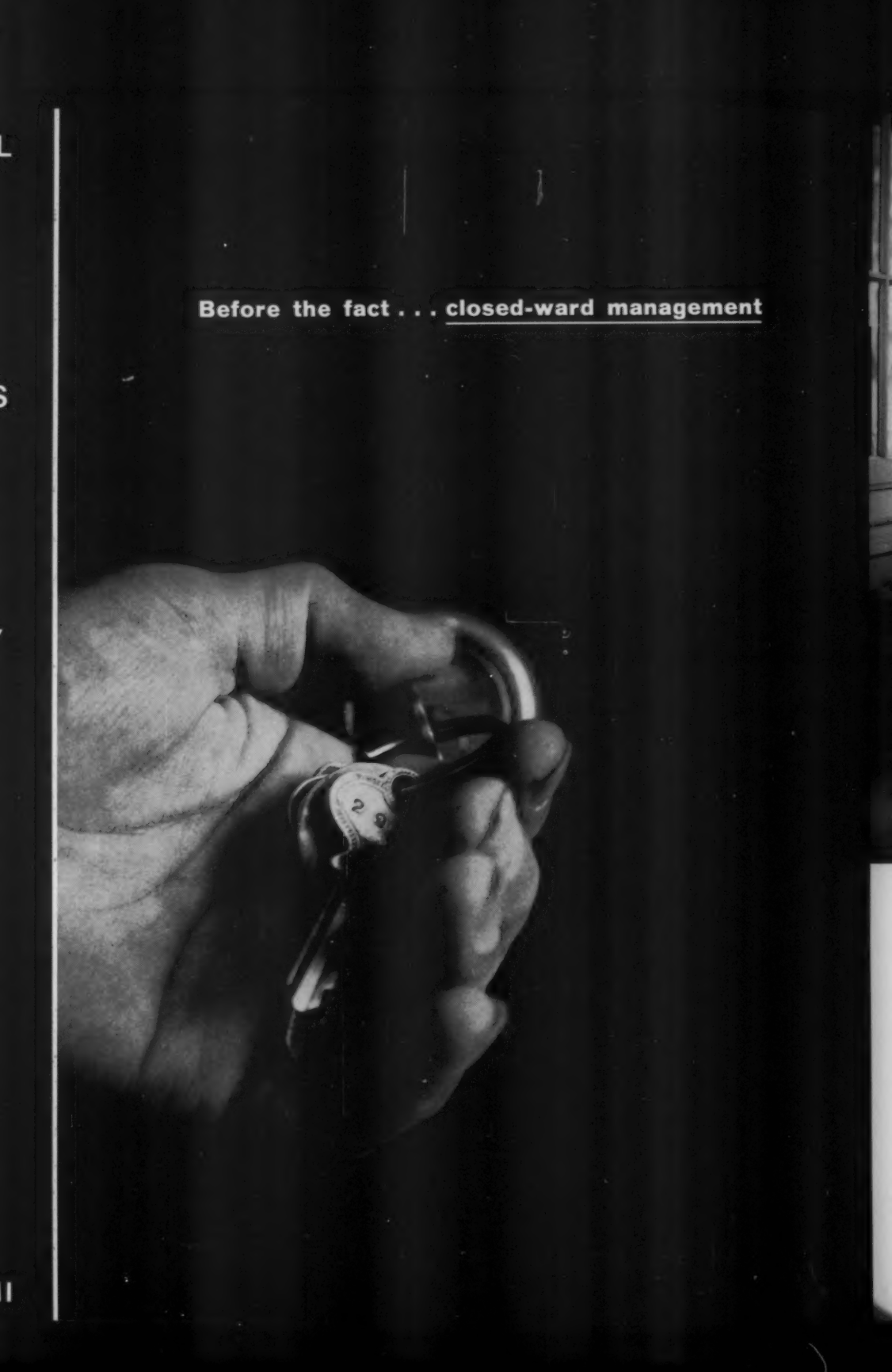
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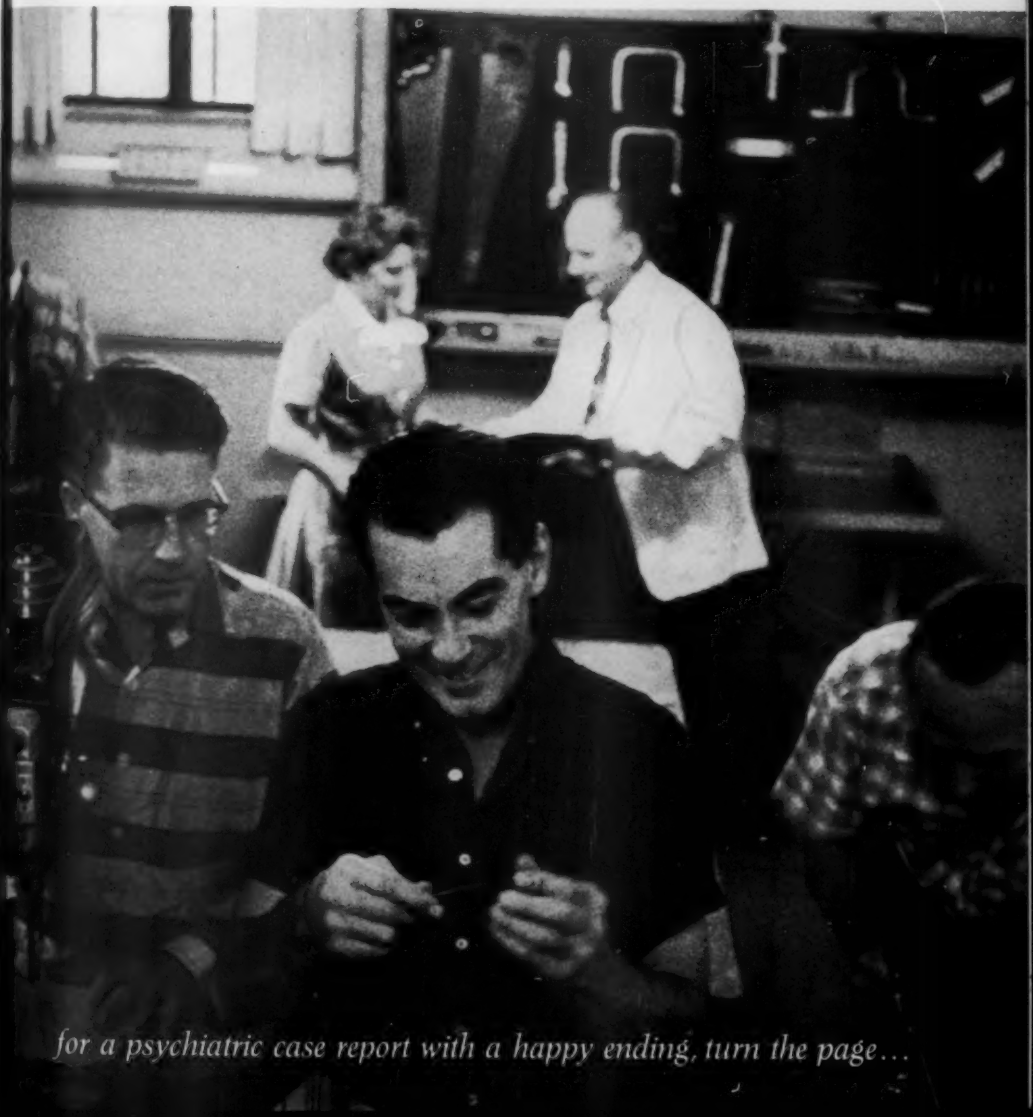
of being "part of things"



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REFERENCES: 1. Scientific Exhibit, 9th Annual Meeting, Am. Acad. Neurology, Boston, Mass. April 22-27, 1957. 2. Blumenthal, L. S., and Fuchs, M.: Special Report on Clinical Use. 3. Berman, B. A.: Current personal communication in the files of Nordson Laboratories. 4. Sanders, S. H.: Current personal communication in the files of Nordson Laboratories. 5. DeJong, R. N., and Jones, E.: Current personal communication in the files of Nordson Laboratories.

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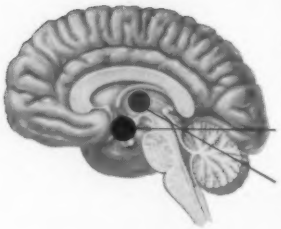

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1. Rinaldi, F., and Himwich, M.E.: Dis. Nerv. System *16*:133-141 (May) 1955.
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5. Case reports on file at Wyeth Laboratories.

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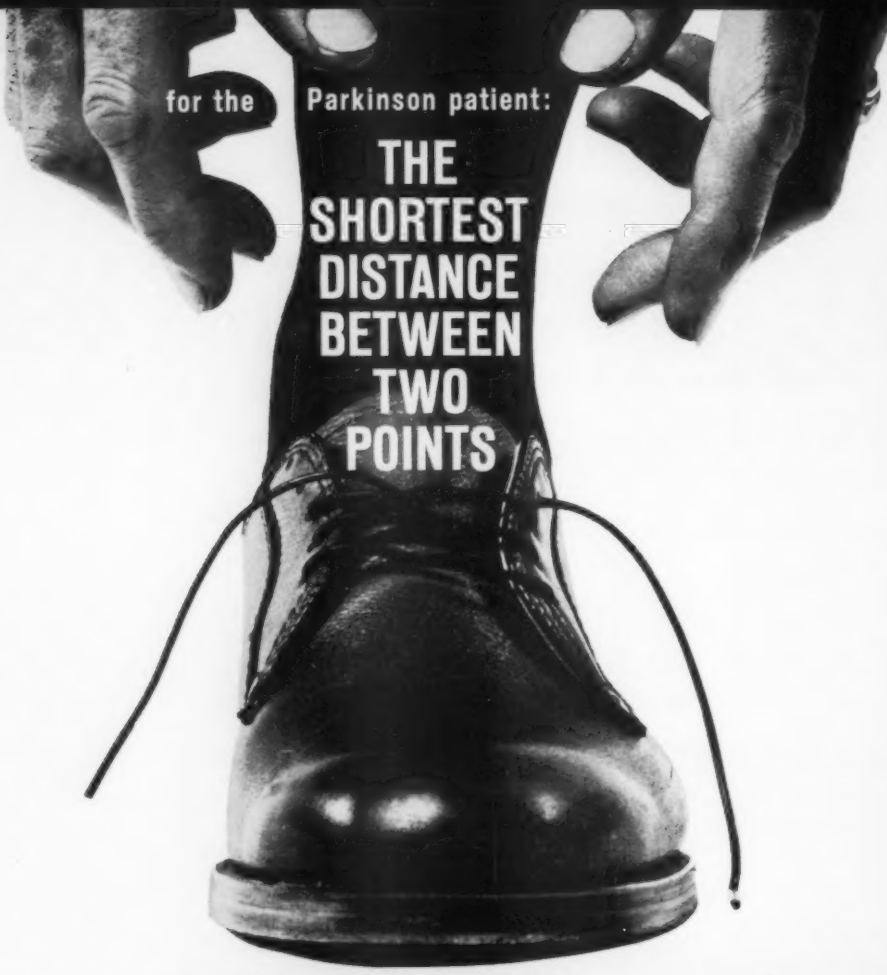

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Neurology Volume 9 • Number 5

Neurologic aspects of porphyria

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PORPHYRIA INCLUDES a group of diseases characterized by specific clinical features and excessive formation and excretion of abnormal amounts of porphyrin compounds. Neurologic manifestations are found only with the intermittent, acute form of porphyria. The present report concerns 2 patients with acute intermittent porphyria studied clinically and pathologically. The clinical and pathologic aspects of the disease as reported in the literature are briefly reviewed.

CASE REPORTS

Case 1. A 44-year-old white woman was admitted to another hospital on November 17, 1953, with right lower quadrant abdominal pain which had lasted thirty-six hours. She described herself as having a nervous and anxious temperament, with occasional episodes of hand tremor, palm sweating, palpitation, mild headaches extending into her neck, and difficulty in swallowing. She denied motor or sensory symptoms.

Physical examination was consistent with the diagnosis of acute appendicitis, and, under Pontocaine spinal anesthesia, a gangrenous appendix was removed on the day of admission. A week later she began to have severe, intermittent, generalized abdominal pain which could not be explained as a complication of operation. Because she appeared markedly apprehensive, barbiturates were given for the first time a day after the onset of pain. On the sixth day of abdominal pain, generalized convulsions occurred frequently. The convulsions were partially controlled by intravenous sodium phenobarbital. On the third day of convulsions, she became stuporous and had increased deep tendon reflexes in the right leg and a right Babinski sign. The patient became more alert three days later and was found to have partial expressive aphasia and right hemiparesis. She improved during the next few days until she had only slight right facial weakness.

Her clinical status then changed; she became progressively apathetic, lethargic, and disoriented and complained of seeing mice on the ceiling and people with red faces. A day later, she developed horizontal nystagmus on lateral gaze, progressive weakness of all 4 extremities, and pains in her legs. The deep tendon reflexes were active throughout, and the right plantar response was extensor. Hypalgesia was present over the left lower trunk and leg, and the muscles and nerve trunks of both legs were tender. She had urinary incontinence.

Within a few days, the patient was stuporous. Although she developed a flaccid quadriplegia, leg weakness predominated, and, in addition, she had bilateral facial weakness, a weak voice, and difficulty in swallowing. Deep tendon reflexes were absent. She had no pathologic reflexes. Hypesthesia to anesthesia was evident below the level of the clavicles over the trunk and in her arms above the elbows. Shallow, rapid respiratory movements were limited to her diaphragm, and she was unable to cough. At no time was she febrile. Penicillin, streptomycin, calcium gluconate, thiamine chloride, and Gantrisin were administered. She was fed by tube.

Following the onset of illness, her urine was

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occasionally dark; a month after admission, urine became dark reddish-brown, particularly when she stood. Qualitative tests on her urine revealed coproporphyrin and uroporphyrin in large amounts. The urine was acid and contained a trace of albumin and rare red blood cells. She had peripheral leukocytosis of 31,000 white blood corpuscles per cubic millimeter. The cerebrospinal fluid was under a pressure of 120 mm. water and contained 22 mg. per cent protein, 3 lymphocytes per cubic millimeter, and 716 mg. per cent chlorides. A culture was negative.

On the forty-eighth hospital day, respiratory paralysis progressed to sporadic gasping breaths. She became cyanotic and had a pulse rate of 140 per minute. She had no signs of respiratory infection. Norepinephrine was given intravenously for a drop in blood pressure, but respiration ceased that same day and she died five weeks after the onset of the neurologic symptoms.

Case 2. A 35-year-old woman was admitted to Jefferson Hospital in June 1944 with weakness of both arms. A month previously, she had had, for a few hours, severe, sharp precordial pain with no associated symptoms. At that time, she was emotionally disturbed, presumably because her husband had just had orchidectomy for a testicular tumor.

Ten days prior to admission, she began to complain of bilateral shoulder weakness which progressed and spread, involving both arms and hands. Within a few days, she had generalized pain in her upper extremities. A tentative diagnosis of hysteria was considered by her local physician and her family. She noticed some weakness of her legs two days before admission. She had no other neurologic symptoms except severe constipation.

On admission, she was apprehensive and had a flaccid paralysis of the shoulders and arms with weakness of hand movements. There was weakness of the lower extremities, absent tendon reflexes in the arms, and diminished patellar reflexes. Abdominal reflexes were absent. The area over the nerve trunks in her arms and legs was tender. Leri's sign was absent in both arms. Hypesthesia was found over C5, C6, and C7 dermatomes and over the L2 areas bilaterally. The clinical impression was radiculoneuritis involving the lower cervical and lumbar roots.

Laboratory studies revealed a normal hemogram, negative serologic tests for syphilis, normal cerebrospinal fluid, and negative x-rays of the chest, complete spine, and paranasal sinuses. A plain film of the abdomen revealed generalized bowel distention with segmental constriction. The urine varied from black to red and contained traces of albumin, but no blood. Abnormal porphyrin compounds were found in the urine in excessive amounts.

The patient's course in the hospital was characterized by progressive weakness of her extremities and trunk musculature. At no time were the cranial nerves involved. Rapid, labored respirations necessitated the use of a respirator. She became incontinent of urine. After two days of delirium, she died from central respiratory paralysis three weeks after onset of weakness of the arms.

PATHOLOGIC FINDINGS

The general autopsy of each patient revealed no pertinent changes other than those within the nervous system. The only gross finding of note in the study of the brain and spinal cord of Case 1 was a small effusion of blood in the subarachnoid spaces over the right frontal pole. Gross examination of the nervous system of Case 2 revealed nothing of significance.

The microscopic findings in both cases were the same and will be reported together. In sections from both the brachial and lumbar plexuses, damage to the peripheral nerves varied from section to section and from fascicle to fascicle. The predominating pathologic process was one of varying degrees of damage to the myelin sheaths. Neither the relation of such a myelin tubule to a blood vessel nor the position of the tubule in respect to the epineurium or perineurium seemed to be of significance in causing the damage. In sections stained with hematoxylin and eosin and with Masson's trichrome, normal myelin sheaths and axons could be found side by side with fibers in which myelin was in the process of degeneration and removal or totally collapsed. This myelin degeneration could be demonstrated as scattered Marchi positive granules within a sheath or within phagocytic cells. In the hematoxylin and eosin and trichrome stained sections, the damaged areas varied from swollen myelin sheaths with fragmented myelin droplets, through various stages of phagocytosis and proliferation of Schwann cells, to complete collapse of tubules (Fig. 1). The axons were preserved in many of the swollen tubules. By means of Bodian's protargol technic, the majority of axons show little evidence of damage, but beading and breakdown occurred, as well as apparent sprouting of newly formed axons in occasional fibers. In general, the degree of damage in the myelin covering was only poorly reflected in the axon (Fig. 2).

No inflammatory cell infiltration was present. Aside from an inconstant hyalinization of blood vessel walls, no vascular damage could be demonstrated. In general, the predominant pathologic change was limited to the myelin of the Schwann sheaths. So far as could be ascertained, this damage bore no direct relation to the nodes of Ranvier but appeared in a random manner throughout the segments available for study. In a few nerve fascicles on cross section, the eccentrically placed myelin within a sheath, whose endoneurium might or might not be fragmented, suggested edema or swelling within the sheaths. This, however, might represent an artefact. In other areas, endoneural connective tissue distinctly in-

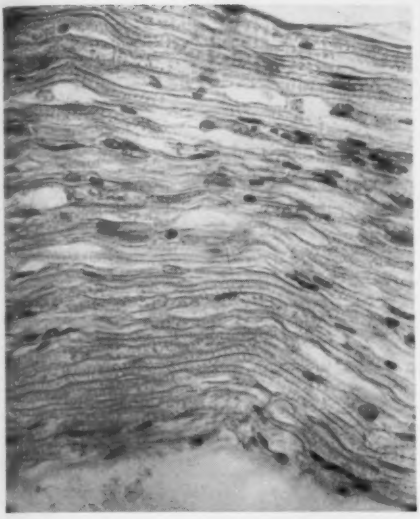

Fig. 1. The peripheral nerve damage varied from intact myelin sheaths and axons to degrees of swelling and vacuolization of myelin, proliferation of phagocytic cells, and collapse of sheaths.

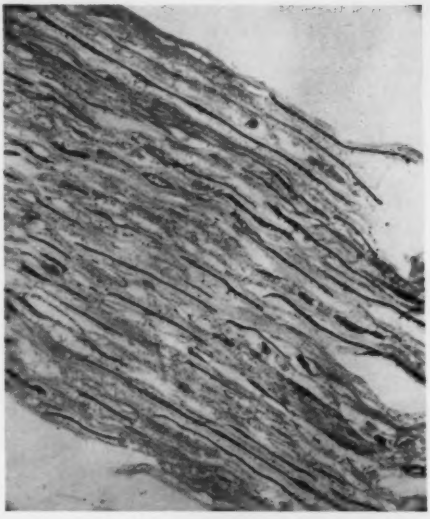

Fig. 2. Bodian stain: Relatively intact axons were found side by side with axons showing varying degrees of degeneration and damage, fragmentation, and bulbous swelling and areas of apparent absence of axons.

creased. This type of myelin degeneration has been described by Gombault as segmental periaxial neuritis.[1] True Wallerian degeneration was present in many of the sections, and axis cylinder damage occurred in addition to myelin pathology.

The changes in the roots were similar to those of the nerves. Along with scattered and spotty loss of myelin, connective tissue and proliferation of Schwann sheath cells and macrophages increased. However, more of the axis cylinders were well preserved than in the nerves, although, in places, the cylinders had a thinned-out aspect. Damage to the dorsal and ventral roots varied from section to section in the 2 cases. No definite statement is possible except to say that the degree of damage in the roots was less than in the more peripheral elements.

In the spinal cords, no evidence of demyelination was found. The only consistent pathologic change was limited to retrograde changes in the anterior horn cells. In various levels of each cord, neurons in axonal chromatolysis could be found with ease among cells which otherwise appeared normal. This damage to scattered anterior horn cells presumably reflected the damage within the peripheral nerves (Fig. 3).

In the brain stem, damage to the dorsal nucleus of the vagus occurred, with loss of ganglion cells and chromatolysis of many of the remaining cells. No other evidence of significant damage was

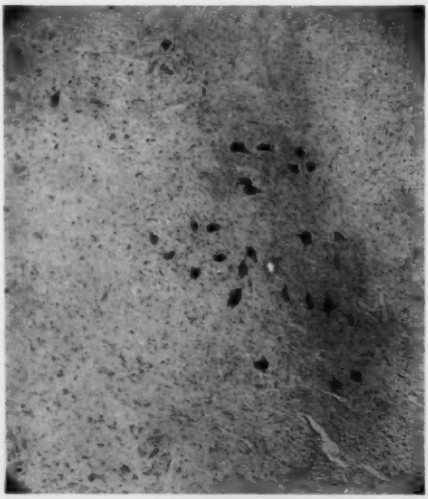

Fig. 3. Neurons showing the changes of axonal chromatolysis occurred in spinal-cord and brain-stem nuclei. Such swollen cells with eccentric nuclei reflected the peripheral nerve damage.

found. The cerebellum, cerebral cortex, white matter, and basal ganglia were all free of significant changes, aside from occasional and diffuse cell loss and congested vessels consistent with the respiratory death.

DISCUSSION

Pathologic changes in patients with porphyria who have clinical involvement of the nervous system have been reported in detail. In 1933, Mason and Courville[2] reported 2 cases and reviewed the literature up to that time. Denny-Brown and Sciara[3] reported the findings in 2 cases and reviewed the literature in 1945. Schwarz and Moulton[4] described the changes in 2 cases and reviewed them in 47 cases in 1954. The neuropathologic changes in 5 cases of acute porphyria were described and discussed in relation to the clinical features of the disease by Hierons[5] in 1957.

As is illustrated by our cases, the most common findings include a nonspecific, parenchymatous multiple neuritis with diffuse cord neuron changes chiefly in the anterior horns. These neuron changes are believed to be secondary to the neuritis, consisting chiefly of swelling and chromatolysis.

Other changes reported in the literature include cytoplasmic pigmentation, cell sclerosis, vacuolization, and severe neuronal disease with loss of cells suggestive of acute toxic ganglion cell disease. To a lesser extent than in the anterior horns, similar nonspecific changes commonly occur in the posterior horns and occasionally in Clarke's column and lateral horns of the cord, the posterior spinal ganglia and autonomic ganglia, the somatomotor and visceral motor nuclei of the brain stem, the cerebellum's Purkinje cells and dentate nuclei, and cerebral cortical cells generally. Variations occur in this basic picture.

A few other abnormalities are occasionally found such as lymphocytic collections around nerve vessels and in sympathetic ganglia, proliferation of dorsal root ganglia capsule cells, slight swelling of astrocytes and oligodendroglia, hyperemia of central nervous system parenchymal vessels, mild acute leptomeningitis, mild subarachnoid bleeding, and yellowish pigment in the white matter of the cerebral hemispheres. Denny-Brown and Sciara[3] emphasized the spotty loss of myelin without interruption of axis cylinders in the nerves that occurred at each node of Ranvier of the spinal roots and the spotty demyelination around arterioles in the brain's central white matter; both are believed due to widespread patchy and intermittent ischemia. No lesion of the vessels of either the peripheral or central nervous system has been described in cases of porphyria.

Other cases of clinical porphyria with neurologic symptoms have revealed no changes in the nervous system. The process in these cases was rapid and was believed to be of a biochemical nature; it produced changes not of a level demonstrable anatomically.[4]

The disease of various forms referred to correctly as porphyria is characterized by the excretion of abnormal porphyrin compounds. The porphyrins excreted are not hematoporphyrin. Hematoporphyrin is the product of the porphyrin part of hemoglobin treated with sulfuric acid after the iron has been removed and which does not exist in nature.[6,7] Classification of these disease forms is based on the site of abnormal porphyrin metabolism. Abnormal porphyrin formation occurs in the bone marrow only in the congenital form and is therefore called porphyria erythropoietica. All the other porphyrias are characterized by abnormal metabolism which results in the formation of increased amounts of porphyrins and porphobilinogen in the liver and are referred to as porphyria hepatica.[7,8,9] The hepatica group includes the intermittent acute type, cutanea tarda or Gunther's chronic type, a combined or mixed form, and latent porphyria. All porphyrias are believed to be due to an inborn error of metabolism with no other known cause. The hepatic forms are familial, appearing first in young adults.[7,9]

Neurologic manifestations are found in only the intermittent acute form and occasionally in the combined form, which actually is a mixture of both the intermittent acute and cutanea tarda forms, although the 2 processes occur at different times. Hepatic cutanea tarda is characterized by the late appearance of photosensitivity and various cutaneous lesions. Hepatic cutanea tarda should not be referred to as chronic porphyria, since all other forms may be chronic. The latent form is of no significance until manifested as intermittent acute porphyria. This porphyria is precipitated

through unknown mechanisms by certain drugs such as barbiturates, alcohol, sulfonal, and triconal and possibly by infectious diseases. Conversion of the latent form into the acute form has been demonstrated experimentally in siblings, and the diagnosis of the latent form may be established if other members of a patient's family have manifestations.[7,9]

The clinical course of intermittent acute porphyria is well illustrated by the cases presented here, as compared with the descriptions in the literature.[3,6,7,9–18]. The course is characterized by episodic symptoms and signs referable to the gastrointestinal tract and/or to the nervous system. The clinical episodes may be frequent or rare, and the manifestations may be progressive or completely remissive, extending over many years or for only several days. Colicky abdominal pain with constipation, and, occasionally, nausea and vomiting, may characterize the episodes alone or usher in the neurologic manifestations. The pain is due to spasms of the gastrointestinal smooth muscle, as illustrated by x-ray studies showing segmental gaseous distention. Since the spasm and abdominal pain can be relieved by autonomic ganglion blocking agents and splanchnicectomy, pain is believed due to an autonomic disturbance.

The neurologic symptoms may be the first and only ones or be associated with the abdominal pain and consist of diffuse cerebral and/or peripheral neuritic manifestations. Flaccid weakness is very common and may be irregularly distributed; usually it is most severe in the extremities and less so in the trunk and muscles innervated by cranial nerves. Deep tendon reflexes become diminished and absent. Bulbar involvement with dysphonia, dysphagia, vasomotor dysfunction, and respiratory paralysis is the usual cause of death. Occasionally, facial and oculomotor weakness occurs.

Sphincter disturbances are sometimes seen. Pain, paresthesias, and tenderness are common in the limbs, but usually little or no objective sensory disturbance occurs. The cerebral manifestations, often the most prominent, may be the presenting symptoms and consist of agitation, depression, disturbance of memory, delirium, hallucinations, convulsions, and impairment of consciousness varying from somnolence to deep coma. During these episodes, overactive deep tendon reflexes and Babinski signs are often seen.

As a rule, the cerebrospinal fluid findings are normal during acute episodes. Lyons[6] reported 1 young man who, in addition to the usual neurologic manifestations, had nuchal rigidity. The cerebrospinal fluid was under a pressure of 240 mm. water, contained 136 mononuclear cells per cubic millimeter, 89.7 mg. per cent protein, and 680 mg. per cent chlorides. No bacteria were seen, and culture was negative. The fluid was clear as usual in this disease. No test for porphyrins was done on this fluid. Watson[7] reports only 1 case with porphyrins in the spinal fluid and states that the presence of porphyrins represents an abnormality of the blood-brain barrier rather than a reflection of abnormal blood levels. Porphyrinemia does not occur in acute intermittent porphyria with any significant degree of neurologic involvement. Porphyrinemia in the form of uroporphyrin I is pronounced in erythropoietica and hepatic cutanea tarda forms in which neurologic disturbance is entirely lacking and, therefore, unimportant as a causative agent of the neurologic manifestations.

Transient blindness may occur in acute episodes and, as has been seen, is thought to be due to retinal artery spasm. Many patients have hypertension and oliguria during the episodes which are thought possibly to be caused by diffuse vascular spasm mechanism. All symptoms may be completely reversible spontaneously. Some observers feel that the mental symptoms occur more frequently in persons with severe neurotic personality disorders or with a family history of mental illness and also that psychic insult, anxiety, and exhaustion are precipitating factors.[12,14]

Functional impairment of the liver or outspoken liver disease is often observed in all forms of porphyria hepatica. Jaundice is seen at times, especially in cutanea tarda. Bromsulphalein retention is usually increased, even without jaundice. The liver reveals varying degrees of fatty degeneration and cirrhosis or hepatic cell injury with excessive amounts of abnormal porphyrins intracellularly.[7,9] Occasionally, clumps of coarse granules of green to yellow-brown pigment, which is not always iron, are seen in the liver.

Available evidence permits no conclusion about the exact relationship of the hepatic disturbances to the porphyria. Because of the outspoken familial incidence and the fact that active disease is precipitated by certain drugs in persons with no manifestation of preexisting liver disease, the liver affection may be secondary to the abnormal porphyrin metabolism within the liver. The degree of liver disturbance in porphyria hepatica is usually minimal compared to the profound hepatic failure associated with coma from that cause.[19]

Persistent tachycardia and muscle weakness between attacks may suggest hyperthyroidism. Rarely, patchy skin pigmentation occurs which is similar to that of Addison's disease. In the intermittent acute type with neurologic manifestations, the death rate approaches 80% within five years after the first episode. The outlook is much better in cases with abdominal symptoms only. No specific treatment exists for this illness. The use of barbiturates and alcohol should definitely be avoided. A brief trial of ACTH is warranted, but, if no improvement is seen in four days, ACTH should be discontinued, since continued use may cause adverse effects. No element of hypoadrenalism has been indicated in the porphyrias.[7] Tetraethylammonium chloride gives relief of abdominal pain, but some people develop hypotension. The powerful blocking agents, such as hexamethonium, are not safe for the treatment of hypertension which occurs in some patients, since the patients are hypersensitive to them.[7] Debilitation and respiratory paralysis are the major problems in management.

Urine in the intermittent acute form contains moderate to great excesses of uroporphyrin I and III as a zinc complex, coproporphyrin III and porphobilinogen. In many cases, only porphobilinogen has been found and others have only slight increase in uroporphyrin. An occasional case has been reported with no abnormal porphyrins found in the urine, but modern definitive testing for porphobilinogen and some of its derivatives was not done.[7,9,20] Since porphobilinogen is the colorless precursor of uroporphyrins and coproporphyrins which are red pigments, the urine may not be abnormally colored during acute episodes.[3,7,9] Most patients notice a darkening of urine at onset. Porphobilinogen is usually present in large amounts during symptomatic episodes, and, if fresh, normal-colored urine is allowed to stand in light, a characteristic red darkening will occur due to formation of the zinc complex of uroporphyrin. Porphobilinogen can be demonstrated by the Ehrlich aldehyde test in which a red compound results that is chloroform insoluble—a characteristic that distinguishes it from the red compound formed by condensation of Ehrlich's aldehyde reagent with bile pigments. Porphobilinogen also produces porphobilin, a dark brown, nonporphyrin pigment which gives most cases of intermittent acute porphyria a dark-brown urine.[7,9]

The basic problem in this interesting, but relatively rare, disease is one of abnormal porphyrin metabolism that involves the nervous system in some way. More than just a better understanding of porphyria has resulted from investigation of this problem, since study has increased our knowledge of the over-all problem of nervous system–metabolic diseases.

In the body, porphyrins combined with iron are prosthetic groups on large conjugated proteins forming hemoproteins; and, therefore, these groups are concerned directly with the transport of oxygen and oxidative processes by which energy is made available to all cells.[13,21] The hemoproteins which contain porphyrins as an essential part include hemoglobin, myoglobin in muscle cells, and the various intracellular enzymes of the 3 groups—cytochromes, catalases, and peroxidases. The porphyrin of these hemoproteins is protoporphyrin which is the end product of various chemical changes after porphobilinogen has passed through the uroporphyrin and then the coproporphyrin stages.[21]

Since coproporphyrin is the only porphyrin excreted in the urine or feces of normal man, an increase of coproporphyrin or the presence of uroporphyrin or their precursor, porphobilinogen, indicates either an abnormal production of hemoproteins with spillover of the porphyrins or a block in the metabolic formation of the hemoproteins. The breakdown of the hemoproteins produces bile pigments of various sorts and not porphyrins.[21]

Several theories exist concerning the possible pathophysiologic mechanism causing the neurologic manifestations of intermittent acute porphyria. The condition is not due to por-

phyrins or porphobilinogen acting directly on the nervous system. The injection of large amounts of porphyrins into animals causes no such lesions.[4] A good correlation has not been made between amounts of porphobilinogen, uroporphyrin, and coproporphyrin excreted and the severity of the disease.[13] Klüver found that the porphyrins of the normal nervous system tissues are coproporphyrin I and protoporphyrin which are present in the white matter of the cord and brain and in proximal portions of some cranial nerves where glial tissue is found. Cytochromes, which contain protoporphyrin, are present in neurons of the cortex, caudate, and putamen; little or no cytochrome or porphyrins are found in peripheral nerves or spinal or sympathetic ganglia.[22,23] Klüver also found no increase in porphyrins in brains and cords of patients with neurologic involvement in porphyria.[24] Furthermore, no neurologic changes occur in the congenital form which has large amounts of porphyrins in tissues and excreta.[7,9,13]

Some investigators propose that the neurologic changes could be the result either of an abnormal intermediate in porphyrin metabolism or the presence of an excessive concentration of a normal intermediate. They propose that porphobilinogen may be the causative agent.[13] This hypothesis is probably incorrect, since abnormal porphyrin metabolism undoubtedly exists in other types of porphyria in which porphobilinogen is not found in abnormal concentrations either in the body or in the urine.[7] Also, porphobilinogen has been identified in urine in association with diseases which can not be classified as porphyria: various liver diseases, malignant diseases of the reticuloendothelial system, metastatic carcinomatosis, tetanus, poliomyelitis, Guillain-Barré neuritis, and rheumatic fever with subacute bacterial endocarditis. Whether these patients have latent porphyria or whether the porphobilinogenuria is secondary is not known. Possibly, the porphobilinogen in these cases is not identical with that of acute, intermittent porphyria.[7,9,17]

Earlier hypotheses that have not withstood later investigation are those that postulate blocking of neuromuscular transmission[25] or ischemic changes due to spasm of smooth muscle caused by some metabolite.[3,4] Some researchers[4] believe there must be a toxic agent acting on the nerve cells and nerves but have nothing more to offer as an explanation.

The most likely explanation would seem to be a profound abnormality in the metabolism of porphyrin compounds involving the intracellular enzymes and reflected in widespread functional changes in the nervous system. This could account for the relatively small demonstrable change in morphology in the brain in most patients and in the nerves of some patients.[13] One group, studying experimentally produced hepatic porphyria in animals by using Sedormid, has shown that liver cells' ability to synthesize catalase is impaired. Lack of catalase could result in the symptomatology. But they have also shown that the porphyrin involved — protoporphyrin — is normally produced by the liver cell, which is unable to construct catalase.[26,27]

The most recent work has shown the existence of a promising mechanism which points to a defect in purine metabolism.[10,27,33] A proportional decrease has been shown in uric acid excretion in experimentally produced hepatic porphyria compared to increased porphobilinogen excretion. Purine and porphyrin have a common precursor, delta-aminolevulinic acid, and a metabolic block at the point where the precursor normally is changed toward purine would result in decreased purine formation. An increase in porphobilinogen accumulation would then result. Purines are found in many coenzymes, which also contain various members of the vitamin B group essential to cellular oxidation processes. Purines also form nucleotides which act as catalysts for enzyme systems and are part of the energy carrying phosphate compounds of the adenylic system.[21] When the vital role of purine in nervous tissues, as well as in other cellular metabolism, is considered, we are tempted to speculate upon the widespread changes which might follow reduced purine formation.

SUMMARY

A report is presented of 2 patients with acute intermittent porphyria and involvement of the nervous system. The clinical picture was that of progressive, peripheral polyneuropathy, predominantly motor in its manifestations. In 1 patient, diffuse cerebral involvement oc-

curred. Both patients died of respiratory paralysis. The pathologic changes were those of a nonspecific parenchymatous neuropathy with associated spinal root involvement of a lesser degree. In the central nervous system, axonal chromatolysis of cells occurred in the anterior horn and vagal nuclei. Nonspecific changes took place which were consistent with respiratory death.

The pathophysiology is considered to be an abnormality in the metabolism of porphyrin and purine compounds. Resulting disturbance of intracellular enzymes is reflected in widespread functional nervous system changes.

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Cerebrovascular disease:

I. The large arteries of the circle of Willis

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DEGENERATIVE ARTERIAL DISEASE has become increasingly important because of its apparently greater frequency in all age groups and because of the rapid rise in the number of older persons in whom these diseases are fairly common.

In spite of a great deal of study within recent years, much uncertainty remains regarding the nature of the causative mechanisms and morphologic aspects of degenerative arterial disease.

Although many studies have been reported on the degenerative arterial changes of the various organs of the body—particularly the kidneys and the heart—very few have appeared on the cerebral arteries. From the few reports available, the frequency of degenerative changes within the cerebral arteries is apparently surpassed only by those within the aorta and the arteries of the heart.[1,2]

Because of the importance of such cerebrovascular changes to cerebral disease and the paucity of such studies in the literature, a systematic study was made of the cerebral arteries of all sizes. Some of the factors that may play a role in the degenerative changes within these vessels were explained.

The present report is a preliminary study in 173 consecutive autopsies of the structure and changes within the larger arteries at the base of the brain.

This preliminary study describes the normal structure and the pathologic changes occurring within these arteries and correlates such changes with factors such as age and sex. However, a much larger series will be necessary in order to adequately correlate these degenerative arterial changes with many of the other possible etiologic factors such as somatic disease, diet, climate, and so on.

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Supported by a grant from the National Institute of Neurological Diseases and Blindness, United States Public Health Service.

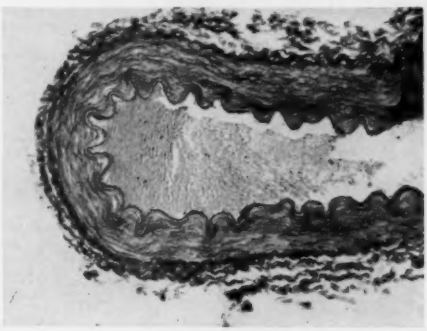

Fig. 1. Normal internal carotid artery. Van Gieson stain × 125

NORMAL LARGE BRAIN ARTERIES

Structurally, all the large vessels are similar in structure and are composed of 3 distinct layers—an intima, a media, and an adventitia. The intima is composed of an internal elastic lamina and a thin layer of endothelial cells.[3,4]

The internal elastic lamina is a wavy, homogeneous layer 5 μ. thick. The normal lamina is uniformly thick throughout and stains evenly (Fig. 1). Generally, the lamina has no defects, except occasionally at the depth of the folds where it may appear fractured but not disconnected. At the bifurcation of the vessels, the lamina becomes split into a thick inner and a thin outer membrane. The thin outer membrane lies on the media.

The endothelial cell layer is very thin and most often lies directly upon the internal elastic lamina. This cell layer is usually composed of a single layer of cells but may show some

Fig. 2. Mild intimal connective tissue increase in the posterior communicating artery. Van Gieson stain × 250

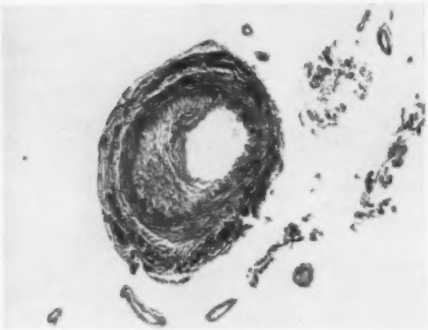

Fig. 3. Marked intimal fibrosis of a small posterior communicating artery. Note the extensive narrowing of the vessel lumen. Van Gieson stain × 100

increase with the formation of areas of multiple cells or of definitely enlarged cells.

The thickness of the media varies and depends on the size of the vessel. In the posterior communicating arteries of 1,200 μ. in diameter, the media will vary from 130 to 150 μ. In the larger internal carotid artery of 2,500 μ., the media usually is 190 μ. thick (Fig. 1). The media is composed of circularly arranged muscle fibers which are often surrounded by a very fine latticework of collagenous fibers. In the normal vessels, these connective tissue fibers are not conspicuous and often are overlooked. The muscle elements extend into the folds of the elastica. A few fine elastic fibrils are also present within the media.

The adventitia normally is very thin and measures between 35 to 40 μ. in all basilar arteries regardless of size. The adventitia is composed of dense bands of longitudinally arranged collagenous fibers. Normally, the adventitia appears to be sharply demarcated from the media. However, careful scrutiny reveals a slight blending of the inner adventitial fibers with the connective tissue latticework within the media.

DEGENERATIVE ARTERIAL CHANGES

Degenerative changes within the large arteries of the brain are common and occurred in over 60% of all our cases, regardless of age. The nature of these changes differs greatly with the size of the artery; the smaller arteries, such as the posterior communicating artery, reveal a consistently different type of change than the larger vessels, such as the internal carotid or basilar artery.

Posterior communicating artery. Very early in life, connective tissue increases within the intima. Thin strands of collagenous fibers are deposited between the endothelium and the elastica interna (Fig. 2). This connective tissue increase can appear in the second decade of life. The connective tissue fibers are usually deposited in a longitudinal direction but may also irregularly fill the inner folds of the inner elastic membrane. This collagenous proliferation may be the only alteration present and may remain arrested without further progression. On the other hand, proliferation may continue to progress and encroach on the lumen—resulting in a markedly narrowed vessel (Fig. 3). Within the intima of these smaller arteries, fatty deposits are uncommon.

The internal elastic membrane may also show early changes which may appear independently or in association with the intimal fibrosis. The earliest alteration consists of a segmental swelling and an irregularity in its staining properties. At the same time, the membrane splits into 2 or more layers. This longitudinal splitting involves only small segments of the elastic layer.

Often, collagenous fibers progressively increase within the media and tend to replace the muscle elements. These collagenous fibers are arranged circularly and show the most extensive increase in the innermost portions of

the media adjacent to the elastica interna. There the collagenous fibers often fill the outer folds of the elastica (Fig. 2).

Ultimately, much of the media may be replaced by heavy bands of collagenous fibers, many of which become acellular and hyalinized. Rather than extending inward from the collagenous adventitia, this connective tissue increase appears to be derived almost entirely from the collagenous fibers already present within the normal media. Occasionally, this connective tissue increase appears only within a segment of the vessel, producing a marked increase in the thickness of the vessel segment. This distorted area filled with collagen may ultimately invade or replace the elastica interna and invade the intima. These large focal areas of connective tissue increase and often undergo vacuolization and hyalinization, but fatty deposits rarely occur.

The adventitia often shows an irregular increase in thickness, and certain segments may be thicker than the media. The adventitial connective tissue continues to maintain its longitudinal orientation (Fig. 2). Often, the adventitial and medial connective tissue fibers are mildly blended but generally the demarcation between these 2 layers remains fairly sharp due to the different arrangement of the connective tissue.

Internal carotid and basilar arteries. A mild connective tissue increase is one of the earliest changes observed within the intima which is similar to that seen in the smaller arteries. An associated increase in the medial connective tissue and a focal increase in the thickness of the adventitia often occur (Fig. 1). At times, the predominant connective tissue change occurs within the adventitia which increases in thickness and sends strands of collagen into the media causing local areas of medial fibrosis. These collagenous changes may become arrested and remain the only degenerative changes within these arteries.

Changes within the elastica interna may occur along with connective tissue increase or may appear independently of any other vessel changes. Segments of the elastica interna become thickened and show definite alterations in staining properties. The inner portion of this membrane loses the ability to stain normally and appears very light, while the outer portion continues to stain deeply with elastic tissue stains. Then the elastic membrane focally splits into many fine strands. This splitting begins from the outer layers of the elastic membrane and may form from 10 to 30 fine elastic strands which may encroach on the underlying media (Fig. 4). This elastic proliferation often involves only a small segment of the membrane; the remaining portions appear structurally intact.

Fig. 4. Marked splitting of the internal elastic lamina. Note the encroachment of this process into the media with a markedly narrowed muscle layer in this area. Weigert's elastic tissue stain × 150

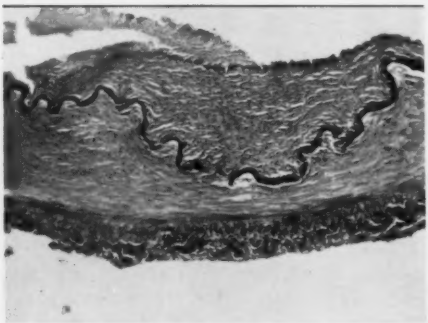

Fig. 5. Focal proliferation of the intima with extensive replacement of the muscle media. Weigert's elastic tissue stain × 200

Continuing to increase in thickness, the intimal connective tissue may replace the underlying elastica interna and produce a focal extension into the media (Fig. 5). This connective tissue finally undergoes hyalinization, frag-

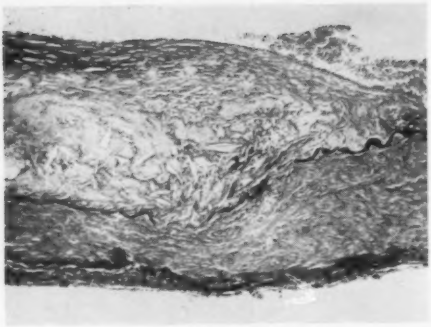

Fig. 6. Severe atherosclerosis of the internal carotid artery. The media is markedly narrowed, and the elastica shows thinning and fragmentation. Weigert's elastic tissue stain × 110

mentation, or vacuolization—chiefly within its deeper layers. Deposits of fatty material soon appear between the connective tissue spaces. The fatty deposits may resemble very fine granules lying loose within the connective tissue spaces or fatty material within phagocytic cells. Ultimately, these fatty deposits degenerate into cholesterol deposits, of which some are soon replaced by areas of calcification (Fig. 6).

Some of the large arteries will show very little intimal change. The predominant change is an increase in the adventitial connective tissue and an associated proliferation of the fibrous elements within the media which may ultimately replace much of the muscle elements.

The degenerative changes described above have already been well documented in the literature. However, considerable difference of opinion remains concerning which of these changes are primary and which are secondary. Most authors agree that atherosclerosis denotes a pathologic change primarily affecting the intima of the larger arteries and is characterized by focal thickenings in which stainable lipoids can readily be demonstrated in and between the cellular elements.

The larger lesions show at one extreme an almost exclusive fibrous composition with only minimal quantities of lipid material, while at the other, these lesions contain lipid accumulations of massive proportions and necrosis. All gradations may be present between these two extremes.

Smaller atheromatous lesions of predominantly fibrous composition may remain unchanged, but the central necrosis of the larger lesions tends to spread in all directions with enlargement of the central area of lipid deposition. As the lesions advance, fibrous deposition becomes more prominent in the superficial layers while lipid-filled foam cells concentrate in the deeper layers. The internal elastic membrane, encroached upon by the necrotic atheromatous tissue, undergoes fraying and fragmentation.[5–8]

Basically, 3 schools of thought have been expressed regarding the primary nature of the atheromatous changes: (1) the primary change occurs within the internal elastic lamina, (2) the first change consists of hyperplasia of the intima with secondary fat absorption, and (3) the fatty deposit is primary and in turn stimulates the formation of connective tissue.

Tuthill[9] studied the large vessels of the circle of Willis and felt that the earliest degenerative change consisted of a splitting of the elastica at the areas of vessel branching. Some proliferation of connective tissue occurred within these areas in patients over 40. Fat absorption occurred secondary to the fibrosis and appeared as small globules in the fibers of collagen or in bipolar fibroblasts which later produced the fat cells. Triepel[10] believed that in youth the internal elastic lamina has a tendency to split and thus introduces the vascular degenerative changes. Allbutt[11] also thought that the earliest atherosclerotic changes appeared in the intima and were associated with changes in the internal elastic lamina which appeared split or multiplied. Eros[12] made an extensive study of 50 brains of psychotic individuals and concluded that the chief and most important alteration occurred in the internal elastic lamina and that all other degenerative changes were secondary. The most conspicuous change consisted of a proliferation of the elastica with resulting reduplication or multiplication of this membrane. In advanced cases, the elastic layers lost their staining properties and were partially or completely replaced by a proliferation of intimal connective tissue. Fatty material appears still later in the proliferated intima.

In 1856, Virchow[13] gave one of the earliest descriptions of the atherosclerotic process—suggesting that the earliest change was an increase in intimal connective tissue resulting from mechanical irritation of the intima by the pressure of blood at critical points. He felt that the thickened intima then interfered with the nutrition of the intimal cells which depend for their sustenance on the plasma of circulating blood. Ceelen[14] also thought that the hyperplasia of the intima was the first change in arteriosclerosis; fat absorption was secondary. Altschul[15] attempted to explain the origin of these connective tissue elements in the intima. He believed that the first change in arteriosclerosis was a regression or dedifferentiation of the endothelium to the mesenchymal stage. The endothelium proliferates by amitosis and migrates into the subendothelial space to form mesenchymal tissue. This mesenchyma then becomes transformed into fibroblasts, resulting in intimal thickening.

The third theory, advocated by Aschoff,[16] Hueck,[17] Leary,[18] Duff and McMillan[19] and others, is that arteriosclerosis is primarily a disease of fat absorption and that all other vessel changes are secondary to or a response to the presence of the fat. Aschoff and Duff and McMillan believed that fatty deposits were derived from the blood lipids and first appeared in the form of fine droplets deposited between the intimal connective tissue lying adjacent to the internal elastic membrane. Leary insisted that the fatty deposits were carried into the arterial intima in phagocytic cells and were not introduced as free lipids which were precipitated into the intracellular spaces. Regardless of how fat is deposited in the intima, these investigators agreed that the presence of the fatty material stimulates the growth of connective tissue as the first step in the formation of an atheromatous nodule.

Our own observations tend to substantiate the second of the above views about primary tissue alteration in atherosclerosis. Certainly, the most consistent and the earliest vessel change was the proliferation of the intimal connective tissue. This alteration was often the only one observed and was frequently present without any associated fatty deposits. Actually, proliferation was the predominant, and usually the only, type of degenerative change observed within the smaller vessels, such as the posterior communicating artery of the circle of Willis.

Even in the larger arteries where fatty deposits were often encountered, the connective tissue proliferation within the intima was often seen in areas where no fatty substances were present. Fatty deposits invariably appeared to be a late occurrence rather than a primary event. Changes in the elastica also were not impressive as an important component of the atheromatous process. Although changes in the internal elastic membrane were often encountered, these alterations by no means preceded the other intimal changes and proliferation of intimal connective tissue often occurred in the presence of an apparently intact elastica.

CLINICOPATHOLOGIC CORRELATIONS

Although our present series only included 173 cases, an attempt was made to correlate our pathologic findings with certain clinical factors, such as the location of the atheromatous lesions, the patient's age, and the patient's sex. Correlation of the pathologic lesions with other clinical factors such as hypertension, diabetes, other somatic diseases, diet, and so on will require a much larger series of cases and will be reported at a later date.

In our present study, the atheromatous lesions were carefully observed on all arteries along the base of the brain. These degenerative lesions were tabulated as varying from 1+ to 4+. A 1+ lesion consisted of a thin plaque involving only a small part of the vessel circumference. A 2+ lesion consisted of a moderate plaque involving over half the circumference of a vessel. In a 3+ lesion, a thick plaque involved the entire circumference of the vessel. A 4+ lesion consisted of a very thick plaque involving the entire circumference and resulting in a marked narrowing of the vessel lumen.

Location of the atherosclerotic lesions. A process as prominent as atherosclerosis of the larger cerebral arteries would seem to have been studied quite thoroughly and described fairly completely. However, a careful review of the literature has revealed very few studies describing the exact location of the atherosclerotic lesions along the basal arteries, even though such observations may well throw some light on at least some of the etiologic factors in this degenerative process. In 1933, Wolkoff[3]

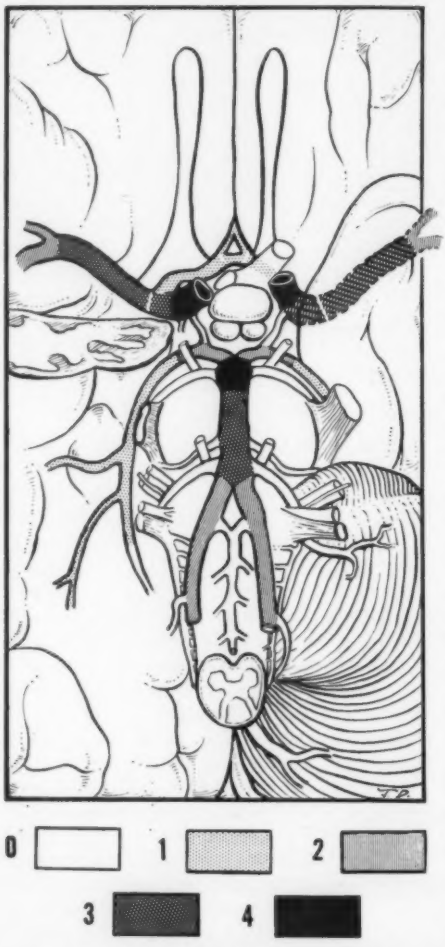

Fig. 7. Distribution of the degenerative lesions on the large cerebral arteries. The severity of the lesions is illustrated by the intensiy of the shaded areas. Note that the most severe involvement has occurred in the upper basilar and internal carotid arteries.

described the distribution of the arteriosclerotic lesions in 98 patients. These lesions occurred most frequently on the internal carotid artery at the bifurcation and along the basilar artery, chiefly at the upper third near the branching of the superior cerebellar arteries. Up to the fourth decade of life, these vessels were almost exclusively involved. After the fourth decade, the atherosclerotic process becomes more widespread, implicating the entire basilar artery as well as the posterior cerebral, and, at times, the anterior cerebral arteries.

Adams and vander Eecken[2] claimed that the atherosclerotic process occurred most frequently in the internal carotid arteries, in the first 3 to 4 cm. of the middle cerebral artery, in the anterior cerebral just proximal to the anterior communicating artery, in the vertebral arteries, in the basilar artery, and in the proximal parts of the posterior cerebral arteries.

In view of the paucity of reports on the distribution of these degenerative lesions in the large arteries along the base of the brain, we undertook such a study in our series of 173 unselected cases (Fig. 7). Regardless of age or sex, the most frequently involved areas are the internal carotid arteries at the bifurcation and the upper basilar artery at the bifurcation of the posterior cerebral arteries. Next in frequency and intensity of involvement were the middle and lower parts of the basilar artery and the middle cerebral arteries, followed by involvement of the vertebral and posterior cerebral arteries. To recapitulate, one can list the intensity of atherosclerotic involvement in the following order: (1) internal carotid arteries at bifurcation, (2) upper basilar artery, (3) middle and lower basilar artery, (4) middle cerebral arteries, (5) posterior cerebral artery, and (6) vertebral arteries. In Table 1, we have listed the frequency of the total involvement and the frequency of the more severe lesions in all the vessels studied. Note that certain arteries appear to be particularly spared from this degenerative change. These arteries are the posterior inferior cerebellar artery, the superior cerebellar artery, the posterior communicating artery, and the anterior cerebral artery distal to the anterior communicating vessels.

We thought it might be interesting to show the relative frequency with which the various vessels were implicated when one considered the severity of the atherosclerotic lesions (Figs. 8 and 9). The various bars indicate the intensity of the atherosclerotic process from a single plaque to cases that had over 16 separate and intense atherosclerotic lesions. In the more se-

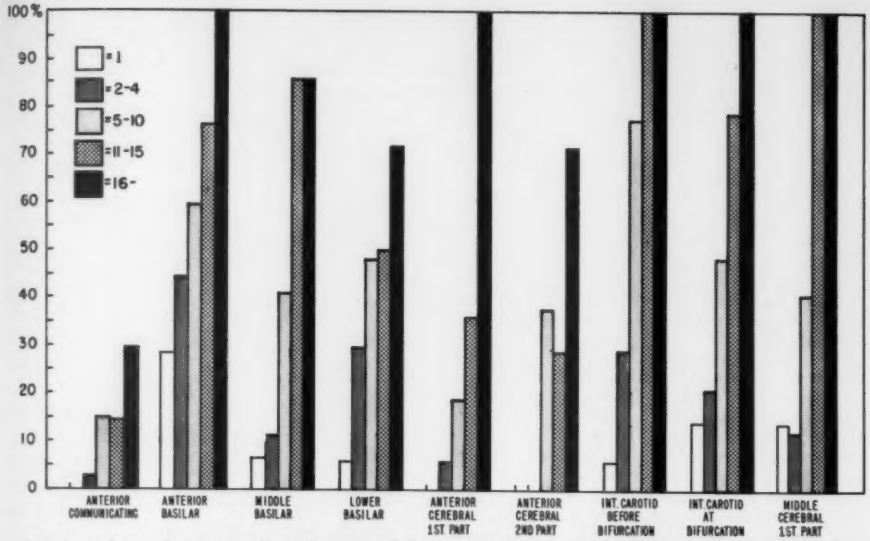

Fig. 8. Relative frequency of involvement of the various large cerebral arteries when compared to the severity of the entire cerebrovascular atherosclerotic process. Note that certain of the vessels along base of brain are always implicated when total atherosclerotic process is severe.

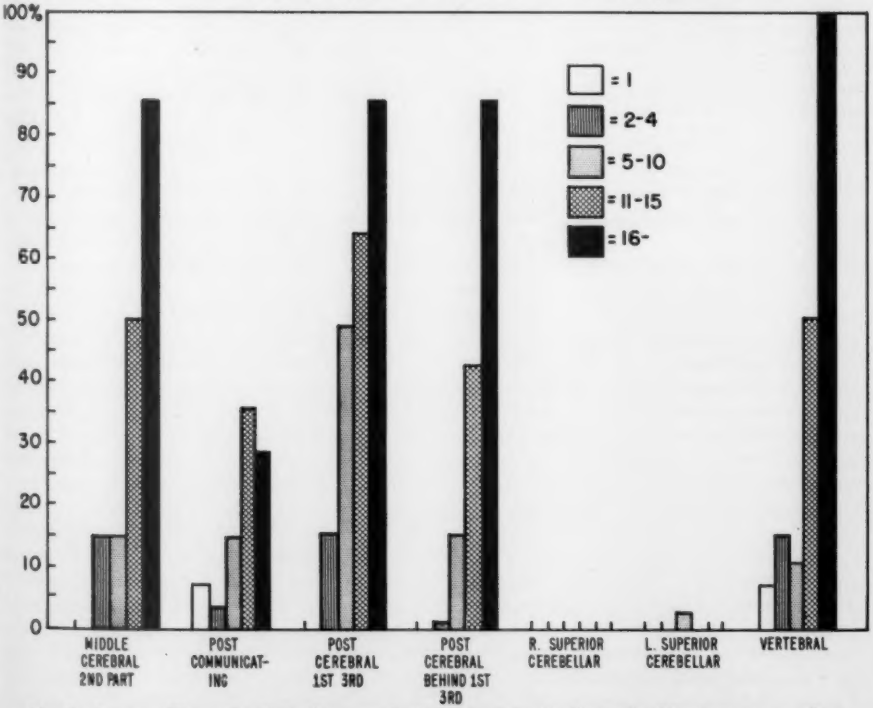

Fig. 9. Same as Figure 8. Note that even in the presence of atherosclerotic changes on other basilar vessels, the superior cerebellar arteries are not involved.

TABLE 1
GENERAL DISTRIBUTION OF ATHEROSCLEROSIS REGARDLESS OF AGE

Location in circle	Total sclerosis			Severe sclerosis		
	Male	Female	Total	Male	Female	Total
Anterior communicaitng	9	1	10	1	1	2
Anterior basilar	33	18	51	10	5	15
Middle basilar	20	15	35	9	5	14
Lower basilar	27	10	37	10	4	14
Right anterior cerebral (anterior to anterior communicating)	10	5	15	3	2	5
Left anterior cerebral (anterior to anterior communicating)	10	5	15	3	1	4
Right anterior cerebral (posterior to anterior communicating)	6	3	9	1	1	2
Left anterior cerebral (posterior to anterior communicating)	5	3	8	1	1	2
Right internal carotid (to trifurcation)	32	19	51	8	4	12
Left internal carotid (to trifurcation)	34	16	50	8	3	11
Right internal carotid (at trifurcation)	20	16	36	6	4	10
Left internal carotid (at trifurcation)	22	10	32	6	2	8
Right middle cerebral (to first branch)	17	17	34	7	4	11
Left middle cerebral (to first branch)	17	8	25	6	3	9
Right middle cerebral (at or behind first branch)	13	8	21	6	3	9
Left middle cerebral (at or behind first branch)	8	4	12	4	2	6
Right posterior communicating	7	0	7	2	0	2
Left posterior communicating	6	2	8	2	0	2
Right posterior cerebral (first third)	22	7	29	5	3	8
Left posterior cerebral (first third)	21	9	30	5	3	8
Right posterior cerebral (behind first third)	9	6	15	3	2	5
Left posterior cerebral (behind first third)	6	6	12	2	2	4
Right superior cerebellar	1	0	1	0	0	0
Left superior cerebellar	0	0	0	0	0	0
Right vertebral	11	10	21	5	4	9
Left vertebral	13	7	20	4	2	6
Right posterior inferior cerebellar	0	1	1	0	0	0
Left posterior inferior cerebellar	0	0	0	0	0	0

vere cases of atherosclerosis—particularly those showing over 10 lesions—certain vessels such as the anterior basilar artery, the first part of the anterior cerebral artery, the internal carotid arteries, and the first part of the middle cerebral arteries were implicated in every single case. Also, the cerebellar arteries were not involved, regardless of the severity of the total atherosclerotic process. Many vessels such as the posterior cerebral arteries, the second parts of the anterior cerebral artery and middle cerebral artery, and anterior communicating arteries were not involved when the atherosclerotic process was mild but did become implicated in more severe cases. Single lesions, when present, tended to occur along the anterior basilar artery, the internal carotid arteries, and the first part of the middle cerebral arteries.

In view of the above findings, one can inquire as to the significance of the localization of these atherosclerotic lesions to the possible etiology of this process. Since the composition of the plasma that bathes the vascular lining is essentially the same, the local discrete distribution of the atherosclerotic lesions may depend upon local differences in the artery wall or upon local mechanical or hemodynamic stresses or trauma.[11,16,18,20]

These investigators felt that continued mechanical strain occurred chiefly at the sites of vascular fixation or bifurcation. Such forces as tension and vibration at these sites resulted in shearing between the intima and media with a loosening of the ground substance which favored a reactive intimal proliferation or inhibition of serum lipids into these areas. Duguid[21] believed that the branches of the main vessels act as a drag on the vessel during systolic lengthening, causing splits and separation of the intima from the media with subsequent intimal proliferation. Benecke[22] believed that mechanical stress was exerted on the vascular wall by the impact of the pulse wave, as well

as by the blood current. Since hypertension is a heightened phase of intravascular tension, Moschcowitz[23] also emphasized the importance of such tension to the atherosclerotic process and pointed out a definite sequential relation between the atherosclerotic process and hypertension. He also felt that, in such cases, the degenerative changes tend to be the most profound at the bifurcations or at points of narrowing.

As one studies the sites of the most intense atherosclerotic changes in our cases, one is unable to accurately correlate such changes with points of vascular fixation. Lesions in the upper basilar artery do occur at the bifurcation of the posterior cerebral arteries where considerable mechanical stress can and probably does occur. However, the lesions of the internal carotid artery do not occur at the point of maximum stress but implicate this vessel anterior to the bifurcation. Certainly, the lesions of the middle basilar and middle cerebral arteries do not implicate vascular branching and, if mechanical stress does play a role, it must be due to an entirely different physiologic process.

The most severe atherosclerotic processes appear to implicate the larger arteries and to gradually decrease in severity as the arteries decrease in size. The most consistent correlation, therefore, that one can make with the atherosclerotic process is with the artery size rather than with the artery branching. It is possible physiologically that the larger arteries are subjected to greater intravascular stress and more readily develop degenerative lesions. Hypertension and arteriosclerosis do seem to have some correlation, although from our present studies, this correlation is impossible to verify. However, one must keep in mind that such a relationship is by no means constant. Hypertension often occurs with no changes in the arteries, particularly in younger age groups. A careful study of the frequency of the atherosclerotic changes in these larger vessels in a large series of patients with and without hypertension as yet has not been made available.

Age in relation to atherosclerosis. Others[16, 17, 24–26] have thought that the atherosclerotic process is the result of a physiologic aging process which may or may not be modified by additional vasoactive factors. Page and Kirk[27] pointed out that these physiochemical and morphologic vascular changes were not related to any appreciable quantitative disturbances in the cholesterol content of the blood, since these hematic components were not consistently elevated during old age. However, many investigators[28–31] have pointed out that atherosclerosis is not a constant phenomenon of old age. Groddeck[32] found that, in 33% of autopsies in subjects over 80 years old, only minimal changes occurred. Additional evidence against the senescence theory is supplied by the not infrequent demonstration of local, as well as generalized, atherosclerosis in children and young adults. Duff and McMillan[19] and Wolkoff[3] seldom found atherosclerotic lesions in the large arteries of the brain in subjects under 30 years old.

A study of our cases shows a most interesting correlation between age of the patient and the atherosclerotic lesions (Table 2, Fig. 10). Undoubtedly, the atherosclerotic process gradually increases with age. This is particularly true with the more severe degenerative lesions (Fig. 10). Interestingly, the atherosclerotic process first appears as early as the second decade of life and rapidly increases in frequency after the third decade. However, 17% of our patients over 60 years old had no evidence of any atherosclerotic lesions. Our tabulation curve for the milder degenerative changes did not progressively increase with age but seemed to level off after the fourth decade so that such mild atherosclerotic lesions appeared to be present in approximately the same frequency in subjects in the eighth decade as in the fifth decade (Fig. 10). This would suggest that a steady turnover probably occurs in patients with mild atherosclerosis; new cases are added as patients with no atherosclerosis develop such changes, while other subjects with mild alterations apparently have progressed into cases with more severe involvement. This explanation would seem to be more logical than the assumption that mild atherosclerotic changes become arrested in their progression. However, possibly this does happen in selected cases.

Because of the occurrence of atherosclerosis in many young individuals and the absence of atherosclerosis in many older subjects, one is

TABLE 2

Age	Total cases	Number and Severity of Plaques											
		0	1	Severity	2 to 4	Severity	5 to 10	Severity	11 to 15	Severity	Over 15	Severity
0 to 9	19—100%	19—100%	0		0		0		0		0	
10 to 19	14—100%	11—79%	1— 7%	3+	2—14%	1+	0		0		0	
20 to 29	8—100%	7—88%	1—12%	2+	0		0		0		0	
30 to 39	13—100%	7—53%	1— 8%	1+	4—31%	1.5+	0		1— 8%	2+	0	
40 to 49	19—100%	12—63%	2—11%	1.5+	3—15%	1.3+	2—11%	3+	0		0	
50 to 59	38—100%	16—42%	1— 3%	1+	12—31%	1.3+	7—18%	1.8+	1— 3%	3+	1— 3%	3+
60 to 69	20—100%	2—10%	3—15%	1+	5—25%	1+	6—30%	1.7+	2—10%	2.5+	2—10%	4+
70 and over	42—100%	3— 7%	5—12%	2+	8—19%	1.2+	13—31%	2+	9—22%	2.8+	4— 9%	3+
Total	173—100%	77—40%	14— 9%		34—21%		28—17%		13— 8%		7— 5%	

forced to conclude that the condition is not necessarily an age change. Atherosclerosis is a disease of the blood vessels more common in older people because of factors which apparently can more easily influence the arteries of these individuals. These factors are due to intrinsic changes in the arteries or to a longer period of action on the vessels which is allowed by subjects in the older age group.

Sex and atherosclerosis. The suggestion has often been made that men are more susceptible to atherosclerosis and that this susceptibility points to the influence of endocrinologic factors in this degenerative process. No detailed comparative studies have been made of sex frequency in atherosclerosis of the larger cerebral arteries. Table 1 shows such a comparison in our series.

In our 173 cases, about 33% were women. Note that the degree of total as well as severe atherosclerosis for practically all the vessels showed an average ratio of about 2 to 1 when the sexes were compared. This would strongly suggest that sex plays very little role in the atherosclerotic process implicating the larger arteries of the brain and that women are implicated as often as men. This would speak against an endocrine factor in the etiology of this degenerative process.

Our present series of cases has not been analyzed sufficiently to allow an adequate correlation with other factors such as hypertension, diabetes, other somatic diseases, diet, infection, race, and so on. Such a survey will be the subject of a later study.

SUMMARY

1] The large arteries along the base of the brain all have relatively similar structure consisting of a well defined internal elastic membrane, a well developed muscular media, and a collagenous adventitia.

2] Regardless of the size of these vessels, the internal elastic membrane almost always measures 5 μ. thick and the adventitia, 35 to 40 μ. thick. The media usually is one-tenth the thickness of the vessel's diameter, although thickness varies, depending on the size of the vessel.

3] In the smaller arteries along the base of the brain, the chief degenerative change consists of an intimal connective tissue increase

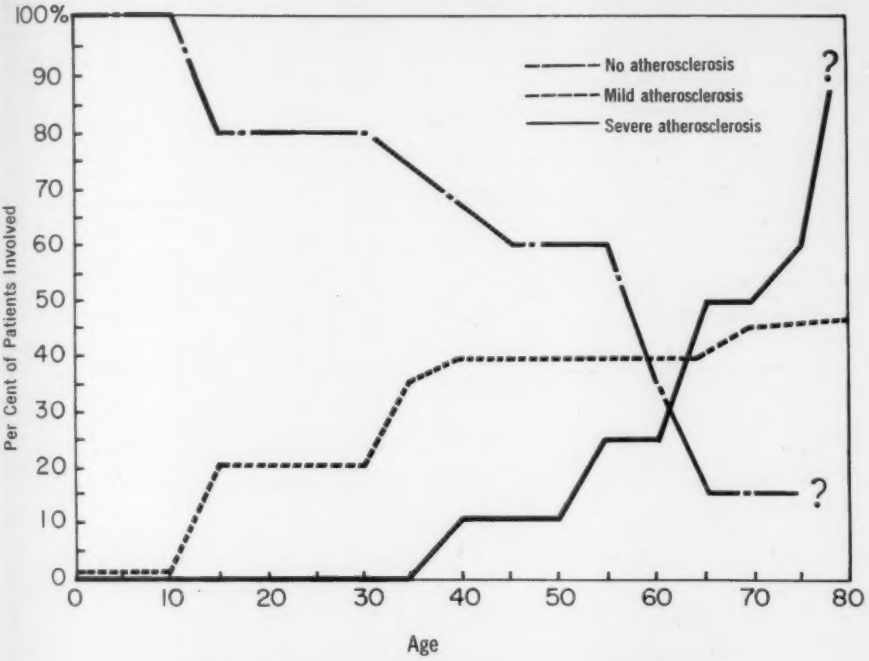

Fig. 10. Correlation of cerebral atherosclerosis with the age of the patient

which may or may not narrow the vessel lumen.

4] The larger arteries reveal not only an intimal connective tissue increase but also show changes within the elastica and fatty deposits within the intima which produce the typical atherosclerotic plaques.

5] Atherosclerotic lesions were most frequent and severe on the internal carotid artery just anterior to the bifurcation and along the upper portion of the basilar artery. Less intense changes were observed along the middle and lower basilar artery and the middle cerebral, the posterior cerebral, and the vertebral arteries.

6] In cases of severe atherosclerosis, the anterior basilar, the internal carotid at and before the bifurcation, and the first portion of the middle and anterior cerebral arteries were always implicated.

7] Frequency and severity of the atherosclerotic process definitely increase with age. Atherosclerotic lesions first appear on the larger intracranial arteries in the second decade of life. Of all subjects in the sixth decade and over, 17% will show no degenerative arterial lesions.

8] Sex plays no role in the atherosclerotic process. Men and women were equally affected.

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Observations of the fundus oculi in transient monocular blindness

C. Miller Fisher, M.D.

ONLY ON RARE OCCASIONS does one have an opportunity to observe the retinal circulation during an episode of transient monocular blindness.

Recently, ophthalmoscopic studies were made during 2 attacks of partial blindness in a patient who had had hundreds of such episodes in one eye. The underlying vascular events were witnessed in greater detail than heretofore reported in the literature. In addition to having their own intrinsic interest, such observations may, by inference, provide valuable information concerning the behavior of the cerebral circulation during transient ischemic attacks associated with cerebral thrombosis.

CASE REPORT

A 54-year-old pharmacist had had recurrent headaches ten to fifteen years before admission. He had developed right hemiparesis two years before which had gradually cleared. For one and a half years, the patient had had brief episodes of partial or total blindness in his left eye once or twice a day. These attacks increased in frequency and duration, and, ten days before admission, he had numbness on the right side of his face, accompanied by complete loss of speech; after this attack, speech did not return to normal.

On examination, the only significant neurologic abnormalities were slight impairment of rapid movements of the fingers of the right hand and reduced pressure in the central retinal artery of the left eye. Attacks of monocular amblyopia continued in the hospital, and, during 2 of these, the patient's retinal vessels were examined ophthalmoscopically. His left carotid arteriography showed marked narrowing of the arterial lumen at the level of the carotid sinus.

The patient's headaches were usually frontal and slightly more on the left side. Although the pain was not unusually severe, the patient had sought medical advice on several occasions. Sleep, as a rule, brought relief, but, a few hours after arising, his headache reappeared and worsened as the day progressed. Often the headaches extended to the occipital region. The headaches felt "deep in" and were usually steady and, occasionally, throbbing. Shaking of the head clearly aggravated them. No one in his family had had similar headaches.

The patient believed that, when he turned his head from side to side while lying down, something in his head "flopped" from one side to the other. As the years passed, the headaches did not become more painful but seemed to last longer and were not as satisfactorily relieved by sleep as before. When the headaches were particularly severe, three years before admission, the patient's blood pressure was found to be over 200. A thorough clinical and laboratory investigation at that time was not remarkable, except for hypertension, and Serpasil and Apresoline were prescribed. His blood pressure gradually fell to normal levels, but he continued to take 0.25 mg. of Serpasil daily.

Two years before admission, while on a hunting trip in the Maine woods, the patient's right arm and hand became numb and weak over a period of one or two weeks. His right leg was also involved, but to a lesser degree, and the hunting trip was not interrupted. Recovery of the leg was rapid, but weakness of the right side of the face suddenly appeared and the patient was unable to speak for several hours. He recovered in a few days and had

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no more similar incidents until shortly before admission.

About one and a half years prior to admission, the patient began to have attacks of partial or complete blindness in his left eye. Although an attack did not occur every day, the patient estimated that 7 to 10 had occurred each week, making a total of at least 700. With the passage of time, the attacks became more frequent and lasted longer. The attacks were similar, but only a few completely blinded the left eye.

Usually the attacks lasted one-half to one and a half minutes, but some lasted forty-five minutes. In a partial attack, only the lower half of his vision clouded over, while in a full attack his vision was completely blacked out and the eyeball felt as if it were being squeezed.

At the onset of a typical attack, the patient first noted a funny sensation in the middle of his forehead, his vision began to fail, and "the muscles of the eye felt as if they were tightening." He likened the failure of vision to the snowing up of a television screen—"a big snow storm clouds out vision." The colorless snowflakes were bright, shining, and jumping. As the cloud took form, he could still see past or through it, but as the cloud became more dense, a total blackout occurred. Vision usually failed over a period of 1 minute; the clouds gradually filled up the lower half of vision first, and, if complete blindess was to come, the clouds extended to the upper part of the field. He had no associated dizziness or lightheadedness. The attacks didn't come at any particular time, and frequently they occurred when the patient was lying down. In this instance, the cloudiness could appear first in any sector of the field of vision, not necessarily in the lower part. His headache seemed to bear no relationship to his monocular blindness.

At 11:00 P.M., ten days before admission, the patient was watching television when the right side of his face became numb. He was unable to speak for 1 minute. Speech gradually returned, passing through a mumbling stage and, although recovery was relatively perfect, a slight degree of slurring remained and speaking was more of an effort. On close questioning, the patient admitted that on approximately 4 occasions in the few weeks before admission, he had felt a twitching of the right cheek, which he had never examined in a mirror. For a minute or so after the twitching ceased, mild paralysis occurred. The patient also described these episodes as "mostly a numb feeling with a few twitches." He had never tried to talk during an attack, except for the episode described above, and, in that one, no twitching had occurred. It was not clear, therefore, whether these episodes were transient ischemic attacks or brief focal seizures.

In the few weeks prior to admission, the patient had had transient diplopia 3 or 4 times; each episode lasted one to three minutes. He had had 2 attacks while driving a car. The images were clearly separated, and one lay above the other. The patient insisted that if he covered his right eye during the attack, he saw double with the left eye alone, while, if he covered the left eye, he saw only one image. He had no associated dizziness, and these attacks were not related to the episodes of intermittent blindness.

At the time of admission he had, as his only complaint, a mild impairment of articulation. Functional inquiry, except as detailed above, was unremarkable. The patient was an inveterate smoker but had stopped using cigarets one month before admission and cigars the day before admission.

Examination. The patient was a healthy-looking, alert, moderately obese man without dysphasia. He apparently was normal intellectually. General examination revealed nothing significantly abnormal. His blood pressure was 150/80 lying down, and pressure did not fall when he stood up. On neurologic examination, he had slight right facial weakness, a trace of dysarthria, and a definite, although mild, reduction of position sense in the fingers and toes on the right. Sensation was otherwise normal in all ordinary clinical tests—pin prick, cotton wool, vibration, cold, and 2-point discrimination.

The patients pupils were equal and reacted to light. Visual acuity on the right was 20/20, on the left, 20/40. The fundi between attacks appeared to be remarkably healthy. Intraocular tension was normal. The central retinal artery pressure was 65/120 on the right, 35-40/70 on the left. Visual fields were full, and extraocular movements were normal. His

tongue and palate did not deviate from the midline. No ocular bruit was heard. Pulsation was clearly reduced in the left internal carotid artery in the neck.

Motor power and rapid alternating movements of his limbs were faultless. He had no cerebellar ataxia. Tendon reflexes were slightly brisker in the right upper extremity than in the left. Plantar responses were flexor. Gait was unremarkable.

The cardiac rhythm was normal, and all pulses were present at the ankles.

Laboratory. Urinalysis: specific gravity, 1,028; albumin, 1+; sugar, 2+; erythrocytes, 2; leukocytes, 15. Blood count: hemoglobin, 16 gm. per cent; leukocytes, 9,800; polymorphonuclears, 63; large lymphocytes, 2; small lymphocytes, 25; monocytes, 7. Sedimentation rate was 11 mm. in one hour. A serologic test for syphilis was not done. Nonprotein nitrogen was 29 mg. per cent; cholesterol, 216 mg. per cent; prothrombin activity, 80%. The cerebrospinal fluid, which was clear, colorless, and under normal pressure, contained no cells and had a protein content of 59 mg. per cent. The colloidal gold curve was 0122321000. A glucose tolerance curve gave the following values in milligram per cent: fasting, 86 mg.; one-half hour, 153; one hour, 193; and two hours, 170.

An electrocardiogram was normal. X-ray of the chest was normal. X-ray of the skull was normal, except for demineralization of the dorsum sellae. An intravenous pyelogram was not remarkable. A left carotid arteriogram showed marked narrowing of the lumen within the carotid sinus (Fig. 1), but the carotid tree filled remarkably well distally. A right carotid arteriogram was within normal limits. An electroencephalogram showed a mild abnormality consisting of slow waves in the temporal regions bilaterally. Pressure on the right common carotid artery during the electroencephalographic examination caused immediate cardiac arrest, and the patient felt faint.

Clinical diagnosis. Partial occlusion of the left internal carotid artery, associated with transient retinal ischemia and old cerebral infarction, was diagnosed.

Course. The patient's course in hospital was uneventful during the first ten days except for 5 attacks of transient blindness of the left eye

Fig. 1. Carotid arteriogram showing partial interruption of the dye within the carotid sinus.

lasting twenty minutes, one hour, one minute, thirty minutes, and sixty-five minutes, respectively. In the first attack, the inferior temporal artery was affected, but in 3 of the other 4 attacks, the superior retinal arteries were involved. Measurements of the pulse and blood pressure made during each attack did not differ from those taken between episodes.

Treatment with Tromexan and Dicumarol was begun twelve days after admission; two days later prothrombin activity was 44%. No further transient attacks of blindness occurred in the next seven months.

OBSERVATIONS OF THE RETINAL CIRCULATION

Observation A. An attack of blindness occurred in 3 quadrants of the visual field of the left eye, which lasted sixty minutes. Ophthalmoscopic changes followed in the last forty minutes.

The patient had finished breakfast at 8:30 A.M. and was sitting in a chair reading at 8:55 A.M. when, over a period of one minute, vision failed in all fields of the left eye except the upper temporal quadrant. Vision had re-

mained unchanged when the eye was examined ophthalmoscopically twenty minutes later at 9:15 A.M. The patient had lain down flat immediately after the attack began.

Twenty minutes. The bifurcation of the central retinal artery, the stems of the superior and inferior retinal arteries, and a short adjacent section of each of the 4 retinal arteries were strikingly white and apparently bloodless (Fig. 2A). The arteries further distal were filled with blood of a normal pink color, and stasis of the column of blood could not be discerned.

Section C (Fig. 2A) of the superior temporal retinal artery appeared flocculated, as if blood cells were settling out or congregating, but no movement was seen. Halfway along this section, a sharp incisure or niche appeared in the wall of the artery and persisted for several minutes, seeming to be the result of the flocculated appearance locally rather than representing an indentation in the arterial wall.

The column of blood in at least 6 venous branches of the superior half of the retina was broken into transverse bands to form a typical cattle truck or boxcar pattern; the interrupted column advanced exceedingly slowly and intermittently but apparently not synchronously with the pulse. The affected veins seemed distended and darker than usual. The inferior retinal veins were not remarkable.

The retina itself showed no significant abnormality at this time or, indeed, during the entire period of observations, except for the mild pallor noted at thirty-five minutes.

Twenty-four minutes (Fig. 2B). The white appearance had cleared entirely from the inferior nasal retinal artery and almost completely from the inferior temporal retinal artery. At *twenty-five minutes* (Fig. 2C), both inferior branches appeared to be normally blood-containing, but the dead-white section of the superior vessels persisted. The boxcar pattern within the veins had diminished, and the flow in the affected veins was quickening. Within a minute or two, the patient stated without prompting that vision in the upper half of the visual field had returned.

Thirty-five minutes (Fig. 2D). The white segment of vessel extended from the bifurcation of the central retinal artery upward into each superior retinal artery but clearly reached at least 1 disk diameter further along the superior temporal branch than it had ten minutes earlier. At intervals of a minute or so, a fine trickle of erythrocytes—the cells were visible almost individually—moved slowly along one side of white segment AB, passing from the column of blood at the bifurcation of the central retinal artery to the column of blood in the more distal part of the superior nasal retinal artery. The flow was intermittent and clearly passed along one side. The trickle of cells was not centrally placed. During this period, the superior nasal artery was definitely attenuated but no flow or flocculation of erythrocytes was seen. The surrounding retina may have been slightly pale.

Forty minutes (Fig. 2E). The column of blood was restored to the superior nasal retinal artery; the white segment had cleared from the artery, but this event was not witnessed. The whitened arterial segment now lay entirely in the first part of the superior temporal retinal artery, reaching almost from its origin to the first bifurcation, a distance of some 3 disk diameters.

The patient immediately said he could see in the inferior temporal quadrant and that blindness was limited to the inferior nasal field of vision. The column of blood in the superior temporal retinal artery was then seen to advance slowly, inching along the vessel and driving or displacing the whitened segment before it. The opposite end of the white segment itself advanced, displacing the distal column of blood farther out along the arterial branches. The advancing column of blood at C moved slowly without any visible pulsation, and no mixing occurred across the red-white interface. The interface appeared to be unequivocally transverse or rectangular, and the white segment of the artery was of exactly the same diameter or width as the red column. The red column did not seem to be advancing by distending a previously contracted channel. The distal end of the white segment formed a flat or transverse interface with the column of blood next to it; no mixing across the interface was seen, and the red and white segments were of the same width.

Within a period of approximately three minutes, the arrangement seen in Figure 2F had been attained: 2 white segments lay astraddle

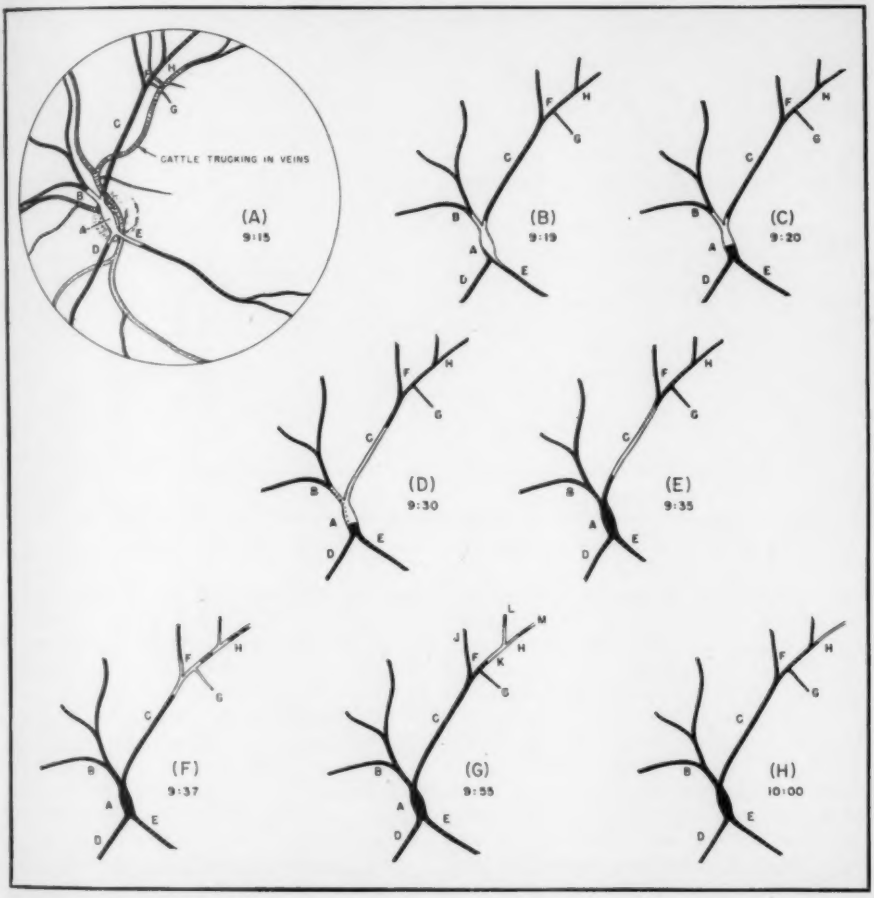

Fig. 2. Observation A. Diagrams of the appearance of the retinal vessels at intervals during the period of blindness (*see text*)

2 adjacent bifurcations, and the column of blood along the larger branch in each case became broken up. For approximately fifteen minutes, no further movement was observed. All fronts or interfaces were flat or square. The small branch G was clearly white. The blood-containing sections of the arteries distal to the white segments were virtually as dark as the veins and definitely distended, although the distention seemed not to determine the movement of the blood to be described below.

Sixty minutes (Fig. 2G). Rather suddenly, the column of blood began to advance once more, moving along the superior temporal retinal artery and passing bifurcations F and H; the progression was extremely slow and gradual. As the red column passed bifurcation F, the whiteness of branch J first receded to the bifurcation, then merged with the white segment of the larger vessel K which was gradually displaced distally by the advancing column of blood. As bifurcation H was passed, the white column receded from arm L and was carried along branch M. (This observation on

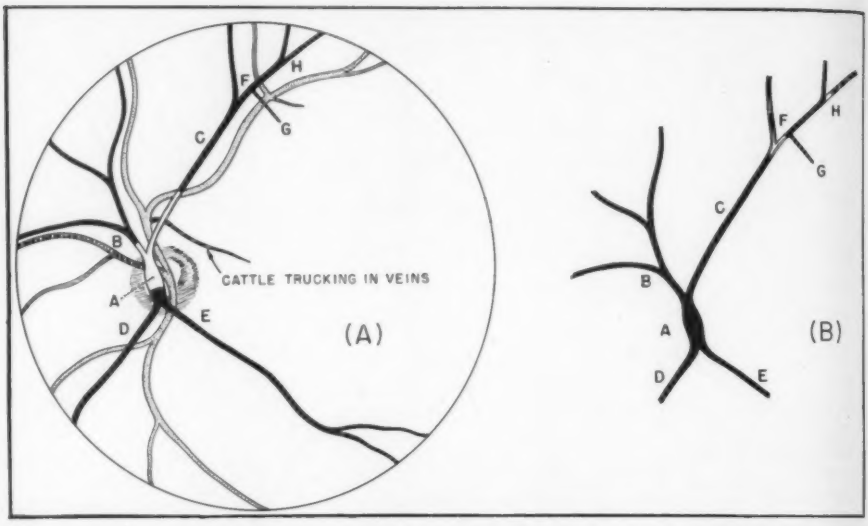

Fig. 3. Observation B. Diagrams of the retinal vessels at 2 stages of partial blindness

the exact behavior of the white segment at bifurcations, although fairly reliable, is put forth with reserve until confirmed.) Finally, the whiteness passed into the most distal branches of the superior temporal retinal artery and was lost from easy view, although 1 observer glimpsed a white fragment after seventy-five minutes. As the involved sections of the artery became red and filled with blood again, the vessels appeared to be quite healthy and a normal light reflex could be seen. As the column of blood was restored at sixty minutes, the patient reported that vision had returned to normal.

A feature of the final migration which might be emphasized is the events in the small branch G. While the white segment lay in vessel K opposite the mouth of branch G, branch G appeared to be as white as the main branch, but, when the advancing red column reached its mouth, the whole vessel G promptly became red; the change from white to red was almost instantaneous along the entire length of G, while in the main arterial branches, K and M, transformation was very slow.

Observation B. This was actually the first episode witnessed, but the observations were less complete than in the second episode described in Observation A. An attack of blindness lasted thirty minutes in the lower field of the left eye. The fundus was observed for approximately twenty-five minutes.

The patient had just finished his supper at 6:30 P.M. on July 30 and was sitting in a chair when he noticed he could not see in the lower half of the visual field of his left eye. The attack seemed to be one of his customary episodes.

When examined five minutes after onset, the appearance of the retinal vessels was remarkably similar to that described in Observation A, except that the white segment lay only in the stem of the superior retinal artery and the adjacent nasal and temporal branches (Fig. 3A). The superior retinal veins showed the broken boxcar pattern, and the flow, which was extremely sluggish, was clearly pulsatile. After one and a half minutes of observation, the inferior part of the white segment began to be replaced by an advancing red column and the white bubble was displaced distally along the superior temporal artery. The white segment moved forward in a pulsating fashion and in seven to ten seconds had reached point C; within a few seconds more, the white

segment lay at bifurcation F and the column of blood distally was interrupted (Fig. 3B). This arrangement persisted for approximately twenty minutes and then cleared completely while the retina was not being observed. The similarity to the events described in Observation A was striking.

SUMMARY OF OBSERVATIONS

Some of the more important features are summarized, with comments on their possible significance:

1] The boxcar pattern and the slow forward movement of the venous column of blood indicated that local stasis had taken place, although a comparable phenomenon was seen to only a limited extent in the arteries.

2] In each instance, the white segment of artery was strikingly white and glistening and neither the pink background of the retina nor the shadow of a vein passing beneath could be seen through this white segment. At times, the lateral borders of the white segment seemed to have a double contour.

3] As the white segment migrated distally, it appeard to be temporarily halted at bifurcations, and our immediate impression was that a pale, intravascular substance had become arrested like an embolus. However, since the whiteness was possibly produced in some other way, the white segment has purposely not been alluded to as representing intravascular material in the descriptions given in Observations A and B.

4] At thirty-five minutes in Observation A, a trickle of erythrocytes seemed to run intermittently along one side of the white segment as if intravascular material displaced the tiny stream to the periphery of the vessel. The restoration of blood flow did not take place through a central narrow channel, as might have been expected if the bloodless arterial segment had been the site of excessive vasoconstriction.

5] The interface between the red and white segments was always rectangular or transverse and did not taper off. Furthermore, no mixing occurred across the red-white interface, and the diameter of the adjacent white and red segments was the same; 4 or 5 observers checked this point, and the red column of blood appeared to be interrupted by a white material within the vessel rather than by a white stretch of constricted vessel. If the latter had been the case, one would not have anticipated that the interface would be square or that the white and red segments would have the same diameter.

6] The forward movement of the red column and the simultaneous *en bloc* advance of the white segment seemed to point clearly to intravascular material being displaced distally by the oncoming blood. Spasm, a process often evoked to explain transient retinal ischemia, was an alternative interpretation. However, the idea that vasospasm might disappear from the proximal end of an affected segment of artery and at the same time appear and advance at the distal end of the segment—remaining unaltered between—would severely test our already too elastic conceptions of the capabilities of cerebral vasospasm.

As already mentioned, the impression gained immediately on observing the vascular events was that a white material, immiscible or relatively immiscible with blood, was being driven distally along the artery. The consistency of such material would seem to have been about the same as blood and its tendency to be arrested at bifurcations and to form a single mass which did not fragment would indicate a certain degree of cohesiveness. This white material did not distend the artery in the fashion of an embolus viewed at autopsy or in formalin-fixed matter. Perhaps an embolus arrested in such a small artery does not expand its walls; indeed, distention of a vessel by an embolus may be a postmortem or fixation artefact. A puzzling feature of the whiteness was its gradual reduction in amount as it moved distally. The amount originally seen seemed to be much greater than that which lay along the superior temporal artery at the fifty-minute mark. Another explanation of the white segment was that it simply represented a collapsed bloodless segment whose wall appeared opaqe. If that was so, the segment was not completely collapsed, since the red and white segments were of equal width while the width of a flattened vessel should be approximately 50% greater than the diameter of the same vessel when filled and rounded. The objection also arises that a collapsed vessel should not undergo reexpansion proximally

while progressively collapsing distally. Furthermore, since the vessel walls were white when the lumen was bloodless, the wall should normally have appeared as a white line along the red column of blood. This was not seen.

In order to find out if a segment of retinal artery appears white when bloodless, many patients were examined ophthalmoscopically while the examiner exerted digital pressure on the globe above the sytolic blood pressure. In none were the walls of the empty arteries white. The retinal circulation in dying patients was watched, and, as the column of blood slowed and fragmented, the arterial walls did not become opaque. However, the occurrence of anoxia, a low intraocular pressure, and a lowered arterial pressure in the choroidal circulation made conditions much different than in isolated occlusion of the central retinal artery. Duane[1] reported the ophthalmoscopic appearance of the fundus oculi in young subjects during amaurosis produced by exposure to 4.5 g in a human centrifuge. As loss of central vision succeeded loss of peripheral vision, the retinal arterioles stopped pulsating and collapsed.

At this time, the arteriolar tree resembled empty fine polyethylene tubing through which the red reflexes from the choroidal circulation could be seen. "The changes were similar to those seen clinically in vessels with areas of focal spasm except that the organic changes were missing in the vessel walls which usually accompany this finding." The absence of these ancillary findings made the picture seen in blackout unique and unfamiliar. At an earlier stage of peripheral visual loss, the entire tree began to open and collapse rhythmically, much as venules pulsate near the disk in a small percentage of normal patients. The pulsations were not the jumping or serpentine type seen in aortic regurgitation. The author noted that blindness occurred within a few seconds of failure of the circulation and vision returned a few seconds after restoration of the circulation. In another observation, Dickson and associates[2] found that, distal to an embolic plug, the retinal arteries were attenuated but not white. All the present evidence is against the idea that the whitened segment of artery merely resulted from the absence of blood from the lumen.

Unfortunately, the opacity of the segments of vein between the red cell aggregates, and the bloodless arterial segments was not compared when the blood column was broken up. An additional oversight was the failure to determine the pressure in the central retinal artery digitally during the attack and to observe the effect of such a maneuver on the red and white arterial segments.

7] Apparently, the great majority of the patient's attacks unfolded in a characteristic way; the lower half of the visual field was obscured first—as blood flow in the superior retinal vessels was compromised first. In 4 of the 5 attacks occurring in hospital, this pattern was followed. It is truly remarkable that ischemia distal to an obstruction—in this case the carotid sinus—should repeatedly tend to take the same pattern in outlying branches of the vascular tree some 15 cm. distant in the retina.

8] Of special interest was the fact that a visual field defect, corresponding accurately to the arterial branches which were blocked, persisted for periods of up to thirty-five minutes (superior temporal branch) when the circulation appeared to be maintained. The retinal arteries and veins distally contained a normal column of blood without any trace of fragmentation or cattle trucking.

This could mean that an adequate flow of blood had actually been restored and that full functional recovery of the ischemic retina required a certain additional length of time, thus accounting for an apparent delay in return of vision. That this explanation is unlikely is shown by the fact that the return of vision in each quadrant of the visual field occurred almost simultaneously with the disappearance of the white material from each of the 4 retinal arteries in succession, clearly indicating that the factor determining blindness was the white material within the vessel.

The demonstration that transient blindness can exist in a sector of retina, most of whose vessels appear normally filled, affords an explanation for the puzzling cases, usually not reported in the literature, in which an eye was examined during transient, unilateral amaurosis and no abnormality found. This finding might be expected if an embolic particle was invisible or if the arterial obstruction lay proximal to

the nerve head. In such cases, light digital pressure on the globe might unmask a failing circulation. Apparently, merely slowing the blood flow without total arrest will produce symptomatic retinal ischemia. In this instance, any flow must have come by anastomotic channels unless blood was still penetrating the central part of the white plug. In both Observations A and B, the blood column was fragmented in the veins when it was uninterrupted in the arteries, an indication that cattle trucking may for some reason be more readily produced in venous blood. Therefore, careful assessment of the circulation in the veins is especially important in these cases.

Previously recorded observations. From 1870 to the present time, 33 descriptions of the retinal circulation during transient episodes of monocular blindness were found scattered through the literature. The ophthalmoscopic appearance of the vessels varied considerably from case to case, but most observers found the arteries reduced to threads. The descriptions are arranged below in 3 groups: (1) cases in which the appearance of the vessels was somewhat similar to the case described in this report, (2) cases in which the retinal arteries were reduced to threads, and (3) miscellaneous cases.

Group 1. Cases in which the ocular findings resembled those in the case presented.

In 1894, Benson[3] described the very interesting case of a 32-year-old man, who for four years had been having sudden complete two-to-five minute obscurations of vision in one or the other eye. Sometimes his whole field of vision was affected, but, most often, only 1 sector of the field was involved. On 3 occasions, the affected eye was examined during an attack. In 1 of these attacks, the largest division of the inferior temporal artery was entirely bloodless for a distance of about 4 disk diameters; the other vessels seemed normal. In a few seconds, the anemic portion of the vessel changed position, moving toward the periphery of the fundus, at times slowly and steadily, at other times in less regular progressions. When the portion reached the next large bifurcation, it disappeared completely, leaving a normal fundus. During the attack, slight pressure on the globe of the eye produced marked pulsation in the central vessels of each eye. Benson attributed the phenomenon to spasm.

Lundie's patient,[4] an 88-year-old man, had a single attack lasting less than an hour; during this attack, the upper division of the retinal artery, for a distance of less than 1 disk diameter, showed an interruption of the blood column, "as one nips an india-rubber tube." The position of this part of the vessel could be traced as a whitish streak, but it seemed entirely empty. As the attack passed off, a fine thread of blood appeared in the portion of the artery previously empty and it soon returned to normal.

In 1907, Zentmayer's[5] Case 2, a 49-year-old man, had a dozen attacks of blindness in the left eye in a period of three days, each lasting about one minute. Ophthalmoscopic examination during an attack showed first a moderate contraction and distinct flattening of the arteries and veins. When the blindness was complete, the arteries became ribbon-like and lost reflex; the veins, particularly the superior branch, became very narrow. After a brief period, the vessels gradually filled and vision returned. The pupil dilated when vision was lost. This case was included in this group because the term ribbon implies that the vessels were not thread-like and also that they probably appeared opaque.

Crisp's[6] patient was a healthy 14-year-old girl, who suddenly noted loss of vision in the lower half of the right visual field. The blindness persisted, and examination showed that the blood column of the corresponding upper temporal artery was interrupted over a distance of about 1/3 the disk diameter, beginning a little beyond the disk. The empty part of the vessel appeared as a white band of the same width as the rest of the vessel and was cut off from the normal portions of the artery by an abrupt transverse interface at either end. The vessel did not change in the next two weeks as the field defect continued. Although migraine was not mentioned, allusion was made to previous, somewhat similar attacks which were interpreted as scintillating scotoma. Although the retinal change persisted, the case is included here because multiple attacks had occurred.

Foerster and Guttmann[7] describe a 34-year-old man who had had repeated attacks of

loss of vision in the right eye. An attack occurred during ophthalmoscopic examination, and, when vision was lost first in the lower field, the vessels running to the upper retina became bloodless for about 1½ disk diameters above the disk. Further distally blood was seen. A severe left hemiplegia was also present. A right cervical and periarterial carotid sympathectomy was performed, and, at operation, it was noted that the carotid artery scarcely pulsated. Apparently, no special importance was attached to this, and the diagnosis of cerebral thromboangiitis obliterans was made.

Group 2. Cases in which the arteries were obliterated or reduced to threads.

In 1897, Wagenmann[8] described the case of a 69-year-old man who had repeated, transient attacks of blindness of the right eye which came on suddenly, beginning at the side or below. Blindness was total; the pupil did not react to light, and ophthalmoscopic examination showed the arteries reduced to fine yellow threads in which no blood could be seen. Mauthner[9] found severe anemia of the retinal vessels in a patient in whom a fluctuating blindness had been present for one and a half hours. Vision returned while the author was seeking the necessary instruments to do an iridectomy.

In Harbridge's[10] 1906 case, the patient had begun to have numerous attacks of blindness in the left eye which recurred about every two hours. On the next and presenting day, attacks occurred every forty minutes and lasted four or five minutes. Examination during an attack showed: "The inferior temporal artery became lessened in caliber until completely collapsed, followed rapidly by the inferior nasal and the superior arteries undergoing the same change; following quickly upon the arterial change the veins underwent a similar process until the entire retinal circulation looked very much like ribbons against the fundus." Weiss[11] reported the case of a 54-year-old man who had been blinded in the left eye by an accident in childhood. For some time he had been having attacks of blindness in the right eye, often 3 times a day. An attack occurred while he was being examined, and, in succession, the arteries and then the veins became empty and became yellowish-white threads. After approximately half an hour, the vessels filled again.

Langdon's[12] patient was a 40-year-old man who had had attacks of monocular blindness since childhood. The episodes lasted three seconds to five or six minutes; each eye was affected with about equal frequency. In an attack, vision gradually became hazy until it was entirely gone; then a hole would appear in the fog (as he expressed it), and vision would gradually return. The blindness persisted after a typical attack, and examination the next day showed the retinal arteries reduced to threads.

Bruner's[13] patient was a 34-year-old man who for a period of seven days had up to 10 attacks a day of blindness in the left eye. The attacks lasted a few minutes. During an attack of blindness, the disk and retina became pale, the arteries were reduced to threads, and the veins assumed a granular appearance due to the breaking up of the normal blood column. In from one to three minutes, the flow of blood in the veins recommenced, at first slowly, then more rapidly, and the arteries gradually returned to normal.

In 1931, Davenport[14] described the spectacular case of a 57-year-old man who was being treated for bouts of stabbing, crampy pain in his limbs and neck, fever, and difficulty in micturition. He began to have sudden attacks of blindness in one or the other eye, which lasted from a few seconds to three minutes and usually were precipitated by looking downwards. Examination of the eye during 3 episodes of blindness showed a fixed, dilated pupil, a very pale optic disk, and arteries so narrowed as to be hard to trace. The blood column in the veins was broken up in the so-called cattle truck way; the segments of blood moved jerkily in different directions in various parts of the system.

Sanders[15] described the case of a 60-year-old man who had attacks of complete blindness in the left eye which usually came on suddenly during walking, leaning over, or turning the head suddenly. The patient had 2 attacks in the hospital while lying in bed.

Group 3. Miscellaneous cases.

In 1874, Raynaud[16] presented the case of a 59-year-old printer who had periodic attacks of lividity of the fingers and hands and, although not at the same time, transient dis-

turbances of vision. Ophthalmoscopic examination during an attack showed constriction of the retinal arteries adjacent to the disk, partial strangulation here and there, and a remarkable venous pulsation. All signs were more pronounced on the left side. Vascular contractions could be seen to come and go. The visual complaints cleared up when the attacks of discoloration of the hands ceased. In Raynaud's Case 2, a 22-year-old man had obscuration of sight and concurrent attacks of cyanosis of the hands. During these attacks, the retinal arteries were narrowed, widening as the attack passed off.

Ramorino[17] reported the case of a 35-year-old man who for about eleven months had had attacks lasting several minutes in which overlapping, colored moving circles moved in from the temporal side and, on reaching the center of vision, produced temporary blindness. Examination during an attack showed that the retinal arteries and veins were empty at the time of blindness. As blood returned to the vessels, vision was restored. Duane's[18] patient was a woman who, three years before, on two successive days, had had an attack of transient obscuration of vision in the right eye without visible abnormality in the retina. An attack occurred two years later in the other eye, and, while central vision was still severely depressed, the author found a small cilioretinal artery running to the macula, absolutely occluded and thread-like.

Hunter[19] described a confrere who suddenly said he could not see; on examination, the retinal blood stream was broken up "like a thermometer that had been dropped." In 1918, Ormond[20] described the interesting case of a French army officer who for about twenty days had 1 or 2 attacks of transient blindness of the right eye which lasted about one minute and were unassociated with headache or high blood pressure. During an attack, the pupil dilated, the optic disk became pale, and the retinal arteries disappeared but the retinal veins remained visible in part. The attacks ceased after about three weeks.

In Hoppe's[21] case, loss of the upper nasal quadrant of the field of vision of the right eye occurred following a fright during advanced pregnancy. The lower temporal artery on the disk, for a distance of ¼ of a disk diameter beyond its margin, appeared to be absolutely empty. During a period of observation of one and a half hours, the blood column was seen at times to retract from the disk and then return toward it. By the sixth day, the previously narrowed portion of the vessel was nearly of full width and vision had improved. Hoppe ascribed the disturbance to collapse of the vessel wall after the temporarily lowered blood pressure was overcome by intraocular tension.

Jamieson's[22] 88-year-old patient had complete anemia of the central retinal artery and its branches for two minutes; the central artery faded into a mere white line. Rosenstein's[23] patient was a 31-year-old woman who for fourteen years had had transient attacks of obscuration of vision at the time of her menstrual periods. The attack was in either or both eyes, usually lasted only a few seconds, occurred 5 to 15 times a day, and was associated with headache, weakness, palpitation, and vomiting. The author examined the eyes on numerous occasions and found the pupil fixed and dilated, the retina pale, and the vessels constricted and empty.

Wagener and Gipner's[24] 1927 Case 2 was that of a hypertensive 45-year-old woman who for ten years had been having short periods of blindness, sometimes complete, at other times sectorial, involving 1 or both eyes. In addition, her fingers became white on exposure to cold and she had peculiar spells of mental confusion lasting two or three minutes without loss of consciousness. While being examined, she suddenly noticed a loss of vision in the superior nasal field of the left eye and the main secondary branch of the inferior temporal artery was seen to terminate abruptly a short distance from its bifurcation. No trace of a vessel was visible beyond this point. "In three peripherally progressing pulses," the vessel became normal and vision was restored. In Case 4, a 20-year-old woman was eating ice cream when she developed blindness in the right upper visual field associated with obliteration of most of the corresponding inferior temporal artery. The blindness was not intermittent.

Mayou[25] examined a man who had had attacks of obscuration of vision with ischemic appearances of the disk and retina which lasted

three to four minutes. At autopsy, a syphilitic subclavian aneurysm and syphilitic heart disease were found. Further details were not given. Law[26] reported the case of a girl who had had 3 attacks of obscuration of the upper half of the field in one eye, accompanied by headache. The inferior temporal artery was empty, and a corresponding scotoma existed. Schiff-Wertheimer and Ballard[27] described the case of a 52-year-old woman who, in May and July 1934, lost vision in one eye and in August and October 1935 suddenly lost vision in the other eye. Total blindness lasted thirty-six to forty-eight hours, but vision was impaired for two weeks and normal vision returned only after four weeks. The vessels during 1 attack were attenuated, and the intraocular pressure was extremely low.

Swett[28] reported an unusual case in which sharp pain and blindness occurred in the left eye while the right antrum was being irrigated. Examination three minutes later showed the fundus to be pale and the arteries completely empty. After a short period of massage, the arteries seemed to take on a rapid clonic dilation and contraction, the column of blood advancing and receding with marked pulsation. This increasing phenomenon seemed to be transmitted to the veins so that the whole disk pulsated. This continued for twenty minutes, and then the pulsation grew less and less until the retinal arteries had completely refilled. The following morning, vision was 20/20.

Marinesco and Kreindler[29] described a case of bilateral occlusion of the carotid artery in which fleeting attacks of blindness had occurred in the left eye. On examination during an attack, the central retinal artery seemed to be in spasm. Autopsy later showed total occlusion of all 3 of the large vessels arising from the aortic arch.

Carpenter and Carpenter[30] reported the case of a 39-year-old man, afflicted with Raynaud's disease for eleven years, who suddenly became blind in the right eye. After three months, he could only discern light in that eye. The retina was pale, and all the arteries appeared as white streaks. Suddenly, while the retina was under observation, a primary artery shot full of blood and divided. Then another arterial trunk, and another, showed this phenomenon in lightning-like rapidity; the appearance suggested the spokes of a cart wheel. The whole phenomenon was repeated every few moments for over two hours and decreased in frequency in the next several weeks. Sie-Boen-Lian[31] described the case of a 34-year-old man who had had attacks of blurred vision in the right eye, short attacks of weakness of the left arm, and paresthesias of the left arm and the left side of the hand. The inferior macular arteries and, later, the superior ones were at times filled with blood, at others, empty. On one occasion, 2 arteries suddenly changed into white columns and returned to normal in a few seconds.

From this brief review, any physician is unusually fortunate to examine more than 1 or 2 patients during an episode of transient blindness. Individual case reports are the rule and so variable are the descriptions that the cases are almost impossible to classify. The most common picture is one in which the arteries are attenuated, reduced to threads, collapsed, in spasm, or have actually disappeared from view. The change may involve any or all of the retinal arterial branches and may extend over the entire length of a vessel or be focally restricted. In 2 patients, only macular arteries were affected. The appearance of the bloodless segment of artery was usually not described in sufficient detail for comparison with the whitened arterial segments observed in the present case.

The mechanism most often invoked in accounting for the retinal ischemia was vasospasm, but usually no underlying pathophysiologic process to which the spasm might be attributed was evident, and the spasm remained unexplained. Widespread spasm is a condition virtually impossible to substantiate by means of the ophthalmoscope, since vessels badly filled from any cause may have a similar appearance; the diagnosis of spasm should therefore be entertained only after a most careful consideration of the data at hand. Embolism was the explanation used in the period shortly after the original description of the embolic phenomenon. In 3 patients the onset of blindness seemed to be related to bending forward.

Raynaud's syndrome, migraine, and assorted systemic disorders were present in a few patients. In 1951,[32] attention was drawn to the occurrence of transient monocular blindness in cases of occlusion of the internal carotid ar-

tery—often as a prodrome to the onset of stroke; since that time, approximately 30 additional cases of the syndrome have been examined personally. Probably, the several different types of picture observed in the retinal circulation reflect a variety of underlying causes.

The events witnessed in our case are certainly not the usual ones encountered in transient retinal ischemia and, indeed, only 2 cases[3,7] bear much likeness to ours. In the second of these cases, as in ours, carotid occlusion was probably present. One would hesitate on this evidence to suggest that the retinal changes seen in our case of transient monocular blindness are a mark of carotid occlusion, but, on the other hand, the fact that a similar observation has been recorded previously indicates that the events described herein are not unique and that one might be justified in making general deductions from them.

Additional ophthalmoscopic observations in 2 patients with transient monocular blindness who were seen at the Massachusetts General Hospital are briefly described.

In a 37-year-old man, clamping of the right internal carotid artery was performed nineteen days after the rupture of an arteriographically demonstrated saccular aneurysm lying at the junction of the internal carotid and posterior communicating arteries. The patient noted, three and one-half hours after operation, that the peripheral fields of vision of his right eye were cloudy or blurred and that he seemed to be looking through a hole. When he first became aware of the defect, central vision was well preserved and he could see the head and shoulders of his nurse, but, as the field of vision progressively narrowed in the next forty minutes, he was left with only peep-hole vision in the affected eye. Vision in the left eye was normal. He had seen no colors, lights, or flashes. Visual impairment lasted for sixty-five minutes; five minutes after vision began to return, he could read very small print and the fields were no longer constricted. At the height of the attack, the arterial blood columns seemed normal in caliber and shade of color, but the venous column was interrupted and formed a boxcar pattern without any pulsating movement. No white segments were seen in the arteries. The manner in which the circulation was restored was not observed. Here is another instance of fragmentation of the venous column occurring at a time when the arterial column appeared intact.

The second patient, a 50-year-old woman with the aortic arch syndrome as a result presumably of atherosclerosis, had been experiencing repeated one-minute attacks of transient blindness of the left eye for approximately six months. The pressure of the central retinal artery was extremely low in each eye. While the patient was in the hospital, the optic fundus was examined during a five-minute attack of absolute blindness of the left eye. "There were slowing and stasis in the retinal veins and arteries with marked interruptions in the blood columns of the vessels."

EVENTS IN THE PRESENT CASE

We can assume that in this patient, partial occlusion of the left internal carotid artery within the carotid sinus was basically responsible for the repeated attacks of transient retinal ischemia and the episodes of cerebral infarction. The lowered pressure in the left-central retinal artery clearly supports this formulation. But, how partial occlusion of the internal carotid artery in the neck could cause brief episodes of blindness several times a week for one and one-half years is difficult to explain. Of course, if local disease of the ophthalmic or central retinal artery were present in addition to the carotid stenosis, the localization of symptoms to the corresponding eye would be much less puzzling.

In the summary of observations, some of the possible interpretations of the arterial events witnessed by the author were briefly reviewed. Vasospasm or excessive vasoconstriction did not seem to be a factor, and several objections were presented to the idea that the white segments were simply stretches of collapsed artery. The whole series of events strongly suggested that whitish material, a microembolus, lay within the retinal arterial system and intermittently migrated distally. The volume of the material was calculated to be only 0.1 cu. mm. approximately.

Since several of the patient's attacks in the hospital occurred shortly after meals, the possibility existed that the intravascular material was lipid in nature, and, during 1 episode of blindness, a sample of venous blood was taken

for lipid determination. The levels were all fairly normal; total fatty acids, 450 mg. per cent; lipid phosphorus, 10.7 mg. per cent; total cholesterol, 270 mg. per cent; and cholesterol esters, 171. The serum was not grossly opalescent. Actually, droplets of fat within a vessel do not usually appear densely white, and the opacity of the retinal arteries in lipemia retinalis is probably caused by a deposit of fat in the vessel wall rather than by the fat-laden column of blood within the lumen. Conceivably, a platelet mass might resemble an opaque white intravascular mass, but the striking malleability of the material, particularly as shown by its behavior at bifurcations, could not be expected in a cohesive aggregate of sticky platelets.

Sludged blood apparently does not form masses large enough to block arteries and would be red in color, not white. Also to be considered is the possibility that an unusually extensive fragmentation of the arterial blood column had occurred—the white material merely representing a column of plasma from which the erythrocytes had been removed, analogous to the pale segments lying between red-cell aggregates seen in the retinal veins during cattle trucking. However, the tendency for the white material to maintain a single uniform mass initially blocking all 4 of the retinal branch arteries and the fashion in which the red cells at one stage seemed to trickle along one side of the white mass are against this formulation, but by no means contradict it.

Possibly, a clot composed chiefly of fibrin would appear white rather than red or black within a retinal vessel. If the material were in fact a coagulum of some kind, many questions come to mind concerning the site at which it arose, the factors responsible for its formation, and so on. Does such material represent part of a deposit which has accumulated at the site of atherothrombosis or does this material form as the result of a slowing of the circulation to the retina? Does it form regularly in relation to atherothrombosis? Is this material intermittently entering the intracranial vessels as well as the retinal arteries? Why in most attacks did the material enter the superior retinal artery rather than the inferior branches? That a kind of secondary microembolism could cause the same clinical picture on more than 700 occasions tests the imagination. The patient was treated with Dicumarol and, after the prothrombin activity had fallen to 30%, no further attacks of blindness occurred in the following five months. The anticoagulant could well have prevented the formation of a mass of fibrin or of fibrin-enmeshed platelets or leukocytes.

In relating our patient's attacks to meals, Mustard[33] has adduced evidence that, during alimentary lipemia, the activity of the first stage of thromboplastin is increased in vivo and parallels an in vitro decrease in the coagulation time. These findings would agree with the hypothesis that a coagulum caused our patient's attacks. In regard to viscosity, Watson[34] was unable to demonstrate an increase in blood viscosity during the period of postprandial lipemia. Many other factors could well modify or even determine events in the retinal circulation: the small size of the involved arteries, the arrangement of the retinal branches, and the geometric pattern formed by the branches with the main stem. Also, the vessels of the retina are at all times subject to intraocular tension—just as the cerebral vessels are gently compressed by the cerebrospinal fluid—and the presence of this extravascular pressure might account in part for the frequency and benignity of the attacks.

Thus far the author has been unable to reach a conclusive interpretation of the vascular phenomena seen in the retina. Before entering into more speculation, further observations should be made. In reporting this case, we hoped that other observers in their rare encounters with similar cases will be enabled to furnish additional data which will contribute to unraveling the essential mechanism of the attacks.

In the introduction, we pointed out that observations of the retinal circulation could be of importance in interpreting cerebrovascular events, especially transient ischemic attacks—formerly called cerebral vasospasm. The subject is too extensive to be entered into fully here, but a few words concerning the problem are in order. These brief transient episodes of paralysis, numbness, blindness, dizziness, and so on have been variously attributed in the past to vasospasm, fluctuation in the systemic blood pressure, progressive thrombosis, multiple embolism, or a diminution in the intra-

cranial circulation related to the upright posture. While some evidence exists for each of these claims, none satisfactorily explains all the recorded facts, and they remain untested hypotheses.

Usually, cerebral atherothrombosis is the underlying cause of the attacks and many times the transient episodes herald the approach of a thrombotic stroke. In the case presented, a decrease in the systemic blood pressure or alteration in the pulse appeared to play no part in precipitating transient blindness; no change occurred in these vital signs during the attack. Furthermore, although the patient lay down flat immediately after onset of blindness, symptoms and signs persisted for an additional sixty-five minutes.

We are tempted to generalize and suggest that intracranial transient ischemic episodes—at least some instances—will also find their explanation in the occurrence of local cerebral embolism or microembolism analogous to the process witnessed in the retinal circulation of our patient. Were such the case, it would be consonant with one of the most striking features of transient episodes, namely, their cessation when anticoagulants are administered—just as Dicumarol treatment put an end to the attacks of transient blindness in the case presented. Substantiation of this principle will no doubt be difficult, and first a need exists to confirm our ophthalmoscopic observations in additional cases of transient blindness.

If we can establish that such a chain of events is operative in the retinal and cerebral vasculature, we can assume that a similar process is probably at work in other parts of the body—heart, limbs, kidney, and so on. Hence, that the subject should be investigated further is of great importance. No doubt light would also be shed on some of the cases of hemiplegia, obviously ischemic or vascular in origin, for which no explanation can be found.

The patient was referred by Dr. F. D. Adams.

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Treatment of myasthenia gravis with prolonged-action Mestinon

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WITH THE RECENT INTRODUCTION of Mestinon (pyridostigmine bromide) and Mytelase (ambenonium chloride), considerable progress has been made in alleviating the weakness of the patient with myasthenia gravis.

Most authors now consider Mestinon, the dimethylcarbamate of 3-hydroxy-1-methylpyridinium bromide, the drug of choice in the treatment of most patients with myasthenia gravis. Mestinon has proved to be more effective than neostigmine because of its longer action and fewer side reactions. However, the search should be continued for effective medications with more sustained, even action.

With both neostigmine and Mestinon, the patient may experience varying degrees of letdown when the medication is completely utilized. The patient is then weak until the next tablet can be absorbed, and ordinary sleep is usually of longer duration than the action of existing medications for myasthenia gravis. Therefore, longer-acting medication is necessary which enables the patient to rest through the night and yet feel relatively strong in the morning. This is particularly true in patients with severe myasthenia gravis who do not gain sufficient strength at night by sleep alone.

Recently, prolonged-action forms of 2 of the existing major medications for myasthenia have been developed: prolonged-action neostigmine and prolonged-action Mestinon (Mestinon Bromide Timespan). This report will briefly explain our findings after over three years' experience using various forms of these preparations.

Prolonged-action tablets of neostigmine bromide were available in 22.5 mg. and 45 mg. sizes, representing 3 half and 3 full doses respectively of the regular 15 mg. neostigmine-bromide tablet. Mestinon Bromide Timespan was supplied in 90 mg. and 180 mg. tablets again representing 3 half and 3 full doses of the ordinary 60 mg. tablets.

The initial preparations were prepared to release multiple doses and consisted of an outer and an inner core; the inner core supposedly liberated the drug at a later hour than the medication in the outer core. However, for the past year, the method of preparation of both 90 mg. and 180 mg. tablets of Mestinon Bromide Timespan has been altered so that the active ingredients are distributed throughout the tablet mass more or less uniformly. This method of preparation utilizes an absorbent and presumably provides for a more uniform release with no provision for a prompt loading dose as was provided in the outer core of the older tablets. These new tablets have a tendency to take on moisture and become fused together, but this problem was solved by packaging each 100 tablets with a silica gel dehumidifier.

A previous report on delayed-action neostigmine and Mestinon made by Schwab, Osserman, and Tether[1] described use of tablets prepared by the older method with inner and outer core. They found that the majority of their patients preferred both prolonged-action neostigmine and prolonged-action Mestinon to the regular dosage forms. They commented that the greatest value of the prolonged-action medication was in eliminating frequent sleep interruptions. Their studies indicated that the average duration of Mestinon Bromide Timespan was approximately six hours.

Our series consists of 6 men and 14 women who were 21 to 70 years old. All had had well-established myasthenia gravis from three to eighteen years. In all patients, the myasthenia

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affected the extremity and/or cranial nerve musculature. No patient with only localized, ocular myasthenia gravis was included in the series because of the difficulty in assessing therapeutic results. In this type of the disease, significantly less response to antimyasthenic drugs often is found than in more generalized myasthenia.

The series was not of entirely random selection; all patients who were selected for treatment were quite intelligent and had a good understanding of myasthenia gravis and its treatment. In addition, these patients had had at least three years' experience in the use and evaluation of the other antimyasthenic medications — including neostigmine, regular Mestinon, and, in most cases, Mytelase.

The patients were all established on what was thought to be an optimum medical regimen at the time the study began. We believed that the evaluation of this select series would be more reliable than a study of a random group of myasthenic patients. In evaluating an antimyasthenic preparation, the subjective opinion of the patient is of paramount importance. On routine examinations by the physician, slight changes in strength are difficult to ascertain objectively. Any change noted might be dependent on the amount of activity and on the time medication was taken prior to examination. The patients were instructed to substitute one of the prolonged-action preparations for their existing medication either throughout the day and/or at bedtime and were informed about the nature of the drug and the objectives of the study.

RESULTS AND DISCUSSION

The prolonged-action form of neostigmine, available in 22.5 mg. and 45 mg. tablets, was given to only 8 patients. As this preparation is no longer available, it will be sufficient to report that only 3 patients felt that their strength improved and that the duration of effect was sufficiently prolonged to make the drug preferable to regular neostigmine. The duration of effect of prolonged-action neostigmine averaged about one to two hours longer than the regular form. No significant increased side reactions were apparent from the prolonged-action neostigmine as compared with the regular tablet.

The major purpose of this study was to evaluate the 90 mg. and 180 mg. Mestinon Bromide Timespan tablets. As indicated earlier, the preparations first used were the 90 mg. tablets made with an inner and an outer core providing for an immediate release of a dose. However, for the past year, Mestinon has been supplied in both 90 mg. and 180 mg. tablets utilizing an absorbent for sustained, even release of the entire contents of the tablet. No study was made of 180 mg. tablets which used the old method of preparation. Mestinon Bromide Timespan was given to 20 patients previously adjusted on varying other medical regimens.

Of these patients, 55% still use Mestinon Bromide Timespan, either alone or in combination with other medication, from one to three years after the drug was first given; 45% thought that the preparation had no advantages over the regular forms of Mestinon or Mytelase. Only 1 patient felt that Mestinon Bromide Timespan was definitely inferior to regular Mestinon or Mytelase because of considerably less strength and greater side reactions.

The duration of effect of Mestinon Bromide Timespan varied from four to twelve hours and averaged six. In general, muscarinic side reactions were no more prominent than with regular Mestinon. Although an occasional patient noticed slightly more prolonged, even action from the sustained-release tablets as compared with the older tablets with 2 cores, none found any truly major advantages or disadvantages in one method as compared with the other. In other words, if a patient found prolonged-action Mestinon better than regular Mestinon during day or night, this was true with either method of preparation. However, our study did not compare the 2 forms of 180 mg. Mestinon tablets, and this conclusion is based on comparing the old form of 90 mg. tablets with the new form of both 90 and 180 mg. Mestinon tablets.

A notable feature of treatment with Mestinon Bromide Timespan was the wide variation of its effect from patient to patient which rendered any statistical evaluation unreliable in predicting its value to any one patient. Although sometimes evident with other antimyasthenic compounds, such variation in re-

sponse seemed much more apparent with Mestinon Bromide Timespan. Thus, several general points emerge which may indicate the true value of this compound more than the analysis of the entire group as a whole.

1] The most consistent beneficial effect of Mestinon Bromide Timespan is its value when taken at bedtime. The drug allows the patient to rise in the morning with strength sufficient at times to allow him to dress before taking his morning medication. After taking Mestinon Bromide Timespan, 2 patients with severe myasthenia who had had to rise during the night to take medication were able to sleep until morning. On other medication, these patients had not had such good strength throughout the night and in the morning. Prolonged-action Mestinon is undoubtedly effective in this regard, and, if for no other reason, this nocturnal benefit makes the compound a valuable addition to the antimyasthenic drugs.

2] The use of Mestinon Bromide Timespan during the day, while usually an adequate substitute for regular Mestinon, is more difficult to regulate. Release at times seemed too slow. The ability to adjust the dose to rapidly changing requirements based on increased activity and so on was less than with regular Mestinon. Some patients felt that they were getting weaker, but this feeling was usually correlated with difficulty in adjusting the dose and the taking of insufficient amounts. However, no serious side reactions resulted from difficulty in dose adjustment.

3] After administering the old preparation of 90 mg. tablets with an inner and an outer core, 3 patients complained that the core was found in the feces. Each patient felt weaker coincident with this and feared that the medication had not been completely absorbed. Schwab and associates, however, similarly noted this and had chemical assays of the core performed which revealed that most, if not all, of the Mestinon had been absorbed from the core. No similar complaints have been made about the newer method of manufacture in which Mestinon is distributed evenly.

4] Mestinon Bromide Timespan administered in corresponding doses of 90 mg. and 180 mg. was approximately equally effective. Some patients felt that one or the other preparation was a little more effective, but the difference did not appear to be significant. Patients who expressed preference for the 90-mg. tablet did not seem particularly concerned when the supply was exhausted and only the 180 mg. size was available.

Schwab and associates noticed that the larger-sized tablet prepared with 2 cores might cause diarrhea and cramps in the early morning. Although occasional patients experienced similar side reactions with proper dosage of the new Mestinon preparations, this was not a significant complaint. An advantage of the newer method of preparation is that the tablet can be broken to give smaller doses while, of course, the tablets based on an outer and an inner core could not be split.

5] As with all antimyasthenic drugs, optimum doses of Mestinon Bromide Timespan varied widely, ranging from 180 mg. per day to 1,080 mg. daily in this series. The dose of prolonged-action Mestinon was not strictly comparable with regular Mestinon. In general, patients needed slightly larger doses of Mestinon Bromide Timespan to give equivalent strength to the regular form. For example, 1 patient who took 12 regular 60-mg. Mestinon tablets (720 mg.) preferred the 180 mg. prolonged-action Mestinon but found that it took 6 tablets (1,080 mg.) to give only slightly greater improvement in strength than that obtained with 720 mg. of the regular form. Side reactions were the same in the 2 doses.

Reduction in the dose of Mestinon Bromide Timespan to doses equal to regular Mestinon resulted in less strength than that obtained with regular Mestinon. This suggests some slight impairment of absorption of the total dose or suboptimal levels. This observation that slightly larger doses of Mestinon Bromide Timespan were required to give equivalent strength to regular Mestinon was noted even in patients who, on seemingly optimum dose, noted no advantage of one preparation over the other. However, the patients, in general, had no significant difficulty adjusting to this slight increase in dose.

SUMMARY

1] Mestinon Bromide Timespan is a beneficial addition to the group of drugs available for the treatment of myasthenia gravis. The preparation will be commercially available in

tablets containing 180 mg. evenly distributed throughout the tablet. This represents 3 times the dose of the ordinary 60-mg. Mestinon tablet.

2] Prolonged-action Mestinon is most valuable in night-time treatment. The drug eliminates the need for sleep interruption to take further medication and leads to better strength in the morning.

3] Some patients feel that Mestinon Bromide Timespan is the best available medication for their myasthenic symptoms during the day, but many patients do not think that the preparation is significantly better in this regard than regular Mestinon or Mytelase.

4] The physician who treats the myasthenic patient should administer Mestinon Bromide Timespan using the same principles of therapy as with the other anticholinesterase drugs.

The patient must understand the nature of the tablet and its potential side reactions. He begins with a tablet of the medication, noting the time and duration of effect. Thus the number of tablets required per dose—and the frequency of dose—will soon become obvious.

5] Mestinon Bromide Timespan is relatively safe and does not offer significantly increased chances of toxicity over and above the other antimyasthenic agents. However, as with all the effective anticholinesterase compounds, the potential dangers of cholinergic crisis must be remembered.

The authors are indebted to Dr. Robert Floody, Hoffmann-La Roche, Inc., Nutley, N. J., for supplying the Mestinon Bromide Timespan and neostigmine tablets.

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The role of estrogens in catamenial exacerbation of epilepsy

John Logothetis, M.D., Richard Harner, Frank Morrell, M.D., and Fernando Torres, M.D.

NEARLY a century ago, Gowers[1] suspected a relationship between epilepsy and menstruation. Since then, several investigators have confirmed this observation and agreed that an exacerbation of epileptic seizures occurs primarily just before or at the time of menstruation.[2–4] During the last decade, however, some controversy has appeared in the literature on this subject. Among various investigators challenging a relationship between seizures and menstrual cycle, Almquist[5] was the first to support his conclusions with a statistic survey. Although demonstrating a definite rhythmicity in the occurrence of epileptic seizures, he maintained that menstrual phenomena are not involved. More recently, however, Laidlaw[6] found unequivocal evidence of catamenial epilepsy in a twenty-five-year follow-up study of the occurrence of more than 33,000 seizures in 50 epileptic women.

Most investigators in the literature maintain that fits exacerbate shortly before or during menstruation in about 50% of epileptic women. In these women, seizures often begin or preexisting attacks recur or become worse at the menarche. The menopause, as might be expected, seems to have a significant, depressant effect on incidence of seizures,[3] while ovariectomy has been reported to relieve human epileptic fits[3,7] and diminish epileptic discharges in animals.[8] There has been considerable difference of opinion regarding the pathogenesis of the catamenial exacerbation of epileptic seizures. The more important theories and observations in this regard will be discussed briefly:

1] Premenstrual psychic disturbances and emotional instability[9] have been thought to be of primary importance in the precipitation of seizures,[10] while others have denied such relationship.[4] Against the psychogenic theory also is the fact that, although psychic premenstrual disturbances usually disappear with the onset of menses, exacerbation of seizures usually continues during the menstrual flow. Moreover, MacKinnon and MacKinnon[11] have shown that psychic disturbances are greatest during the luteal phase of the menstrual cycle, at which time Laidlaw[6] has found the seizure incidence to be lowest.

2] Water retention, which is common before menstruation[12–14] and partly responsible for the symptoms of premenstrual syndrome,* also has been considered as a possible etiologic factor of seizure precipitation.[4] Although it has been reported that an excess of body water induces seizures in epileptic patients and restriction of fluids tends to reduce the number of spells,[17] water retention has not yet been proved to be a primary cause of menstrual exacerbation of seizures. Ansell[4] could find no correlation between degree of weight gain, edema, and sodium retention and severity of fits in "menstrual" and "nonmenstrual" groups of epileptic women. Such a lack of over-all correlation does not eliminate fluid retention as a factor in precipitating seizures in some

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Read at the tenth annual meeting of the American Academy of Neurology, April 25, 1958.

*Such water retention associated with sodium retention is thought to be mediated either by an excess in the circulating estrogens or faulty luteinization leading to unopposed action of estrogens.[15] This is supported, in part, by several experimental demonstrations of a sodium- and water-retaining effect of estrogens.[14,16]

patients. However, in patients without retention, other epileptogenic agents must be involved.

3] Progesterone recently has been implicated as a factor governing the occurrence of fits during the menstrual cycle. Laidlaw[6] has demonstrated a consistent midluteal reduction of spells and exacerbation near the menstrual period, concluding that his findings suggested an anticonvulsive effect of progesterone during the midluteal phase; withdrawal of progesterone as menstruation approaches leads to the exacerbation of seizures. Earlier workers[18,19] demonstrated that progesterone and some other related steroids have anticonvulsive properties in animals. Desoxycorticosterone, which is closely related to progesterone, has been reported to exert an anticonvulsant effect in epileptic persons.[20] Although the latter studies support the theory of Laidlaw in regard to anticonvulsive action of progesterone during the luteal phase, the evidence for catamenial exacerbation resulting from withdrawal of progesterone is not conclusive.

4] Also under consideration is the role of estrogens in the genesis of catamenial seizures. Before undertaking the present study, we observed aggravation of seizures in a small number of patients given estrogenic hormones premenstrually in an attempt to control catamenial seizures. The aggravation then was suspected to be due to the accentuation of a preexisting unfavorable physiologic environment immediately responsible for the catamenial increase in fits. The unfavorable environment was thought to be produced by the immediate premenstrual hormonal changes characterized by estrogenic predominance. Such increase in estrogenic activity, as reflected in the production of the premenstrual tension syndrome, has been reviewed by Rees.[15]

If a convulsive estrogenic effect could be demonstrated, the premenstrual exacerbation of fits could be attributed to the action of estrogens on preexisting epileptogenic foci. Such a concept appeared possible to us and is our present working hypothesis.

MATERIALS AND METHODS

This investigation concerns primarily the role of estrogens in the etiology and pathogenesis of catamenial exacerbation of epilepsy. First, however, we shall present Part I of our investigation, which consists of some clinical observations in 25 patients aged 16 to 45 years with a history of aggravation of seizures about the time of menstruation. An attempt was made to determine possible clinical and laboratory correlations, aided by records of the date, number, and severity of seizures.

Part II of our investigation concerns electrocorticographic experiments in rabbits and electroencephalographic studies in human beings administered estrogenic substances by various routes.

• Studies were done in 5 rabbits with epileptic lesions and 1 with an intact cortex. Premarin,* a preparation of water-soluble conjugated estrogens, was injected intravenously into the animals in doses as large as 40 mg., and the effect was observed for several hours. In addition, Premarin, 0.0001 to 1% solutions, was applied directly with small pieces of filter paper or cotton pledgets over the intact cortical area of the normal rabbit and epileptic lesions of the abnormal animals. One of the epileptic rabbits had an acute cortical lesion, and the others had chronic areas of discharge. Acute lesions were produced by spraying ethyl chloride on a small exposed cortical area, as described by Morrell and Florenz;[21] the effect of the hormone was determined three to five hours later. Chronic epileptic lesions were produced by the same method one month before the experiment. The electric phenomena were recorded using 4 surface cortical electrodes applied over symmetric anterior and posterior cortical areas, including the site of lesion.

• Intravenous Premarin, 20 to 40 mg., was given to 16 epileptic patients aged 16 to 47 years while electroencephalograms were being made. Of these patients, 9 were from the group of 25 studied in the first part of the investigation. The remaining 7 were unselected epileptic patients, all of whom but 1 were females.

RESULTS—PART I

Observations in catamenial epilepsy. The clinical data are summarized in Table 1. Of the 25 patients, 64% had onset of seizures about

*Supplied by Ayerst Laboratories

TABLE 1
OBSERVATIONS IN CATAMENIAL EPILEPSY IN 25 PATIENTS

	Number of patients	*Per cent*
Onset with menarche (± 3 years)	16	64
Premenstrual syndrome or irregular menses	14	56
Predominance of nocturnal seizures	12	48
Defective libido or infertility	3	12

the menarche. This appears significant when compared with the general female epileptic population and is in agreement with previous observations. More than half of the women previously had had menstrual difficulties—premenstrual syndrome or irregular menses. Also, almost half reported a predominance in nocturnal seizures.

An accurate record on the incidence of fits was kept in 10 of the 25 women with histories of catamenial exacerbation of seizures. The results are presented in Table 2. Apparently, the spells tend to cluster during and immediately before menstruation. The difference in seizure incidence between the premenstrual-menstrual and postmenstrual-intermenstrual periods, although of no great statistic significance ($P > 0.05$), strongly suggests that the catamenial exacerbation starts one to four days before menstruation and disappears with the passing of menses. This observation agrees with previous reports discussed elsewhere in this paper.

None of the other factors studied—glucose tolerance test, fasting blood sugar, pneumoencephalogram, serology, spinal fluid examination, and serum calcium and phosphorus—gave a significant correlation. In 10 patients, investigation of the basal metabolism, urinary excretion of 17-ketosteroids, and follicle-stimulating hormone at the time of menses and midcycle period revealed no significant deviations from normal.

A single patient (the fourth in Table 2) in the group had serial electroencephalograms made at different phases of the menstrual cycle. On Figure 1, it is seen that a moderate dysrhythmia at the luteal phase (A) is exaggerated on the first day (B) and third day (C) of menstruation, at which time slow paroxysmal waves appear in both hemispheres. One day after cessation of menses, the record appears less abnormal (D). Such aggravation of preexisting convulsive discharges at the menstrual period also was noted by Lin and associates.[22] Dusser de Barenne and Gibbs[23]

TABLE 2
INCIDENCE OF SEIZURES IN CATAMENIAL EPILEPSY

Patient	*Number of spells*	*Follow-up period (Months)*	*Premenstrual*–Menstrual (Per cent)*		*Postmenstrual†–Intermenstrual (Per cent)*	
1. M. E.	26	10	28	15	31	27
2. W. A.	122	28	20	32	13	35
3. K. E.	11	6	0	82	9	9
4. C. I.	102	33	31	8	22	39
5. E. D.	44	10	39	11	16	34
6. P. S.	111	9	36	54	0	10
7. E. M.	18	24	55	5	27	13
8. H. P.	25	25	50	44	5	4
9. M. K.	28	6	25	18	11	46
10. S. L.	19	4	63	37	0	0
Mean per cent			35	30	13	22
			65		35	

*Four-day interval before menses †Four-day interval after menses

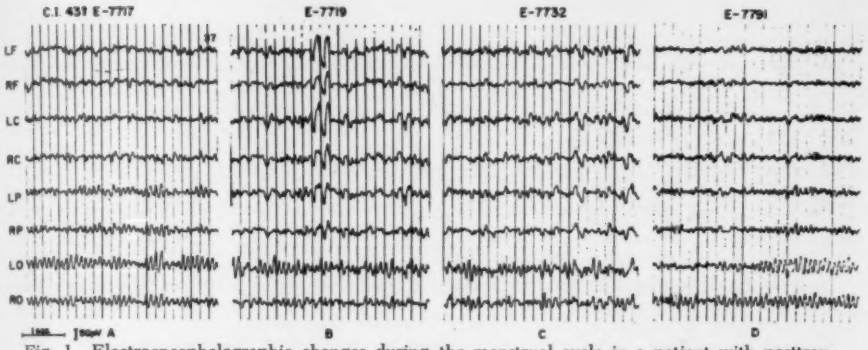

Fig. 1. Electroencephalographic changes during the menstrual cycle in a patient with posttraumatic epilepsy. (A) Eight days before menses. (B) First day of menstrual flow. (C) Third day of menstrual flow. (D) One day after cessation of menses. (See text for more explanation.)

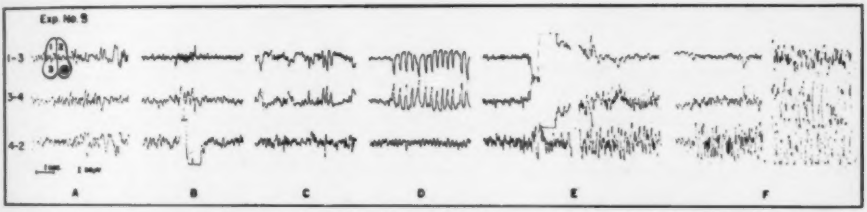

Fig. 2*a*. Electrocorticogram of a rabbit after direct application of Premarin over a chronic epileptic lesion in the right occipital area. (A) Basic record shows spikes of moderate voltage. (B) Effect of diluent alone. (C) Increase in spike activity with 0.1% Premarin. (D) Bursts of slow spikes in opposite homologous site to the lesion thirty seconds after 0.2% Premarin. (E) High-frequency spikes at the site of lesion after 1% Premarin. (F) Grand mal seizure after repeated applications of 1% Premarin

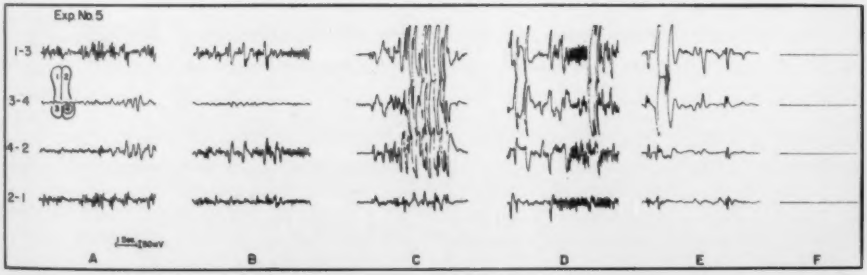

Fig. 2*b*. Electrocorticogram of a rabbit with a chronic epileptic lesion in the right occipital area after intravenous injection of Premarin. (A) Basic sleep record shows depressed voltage at site of lesion, with superimposed paroxysmal slow waves. (B) Higher amplitudes obtained two hours after 20 mg. of Premarin. (C) High-voltage spike discharges fifteen minutes after second injection of 20 mg. of Premarin, or three hours after first. (D) Grand mal seizure seventeen minutes after second injection. (E) Postictal record. (F) Electric silence and death twenty-one minutes after second injection, or three hours and twenty-one minutes after first

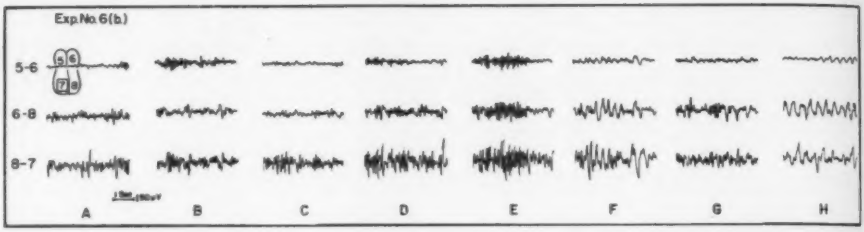

Fig. 3*a*. Electrocorticogram of a rabbit after direct application of Premarin over an intact left occipital cortex. (A) Basic record. (B and C) No electric change with 0.0001% and 0.001% Premarin, respectively. (D and E) Increase in amplitude of posterior leads three minutes after 0.01% Premarin and thirty seconds after 0.1% Premarin, respectively. (F and G) Some decrease in frequency with 0.2 and 1% Premarin, respectively. (H) Further slowing over posterior derivations after repeated applications of 1% Premarin. These changes were felt to be outside the normal basic activity of this animal.

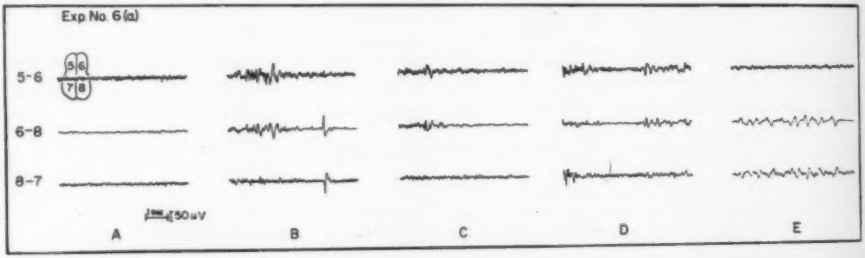

Fig. 3*b*. Electrocorticogram of a rabbit with an intact left occipital cortex after intravenous injection of Premarin. (A) Awake basic record. (B to E) Activity after 40 mg. of Premarin. The electric pattern is more or less similar to the basic record.

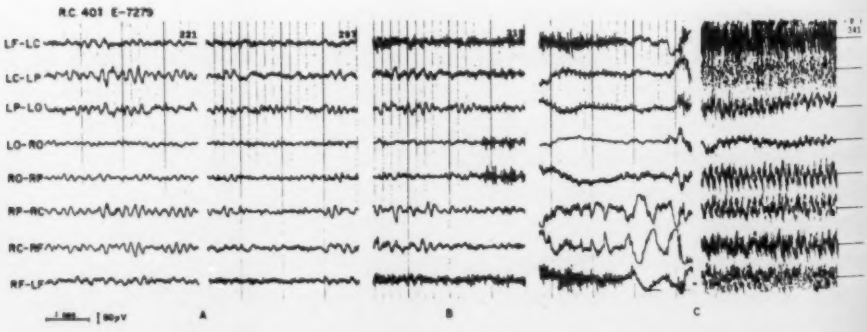

Fig. 4. Precipitation of a seizure by intravenous injection of Premarin in a patient with posttraumatic focal epilepsy. (A) Basic record showing paroxysmal bilateral high-voltage activity. (B) The abnormality is localized in right central area five minutes after 40 mg. of Premarin. (C) Grand mal seizure fifteen minutes after injection

found, in addition, a rather significant change in the electroencephalograms of normal females with the onset of menses.

RESULTS—PART II

Animal experimentation with estrogens. Local application of Premarin over and around the intact cortex of 1 rabbit and cortical epileptic lesions of 5 rabbits resulted in consistent electrocorticographic changes. Plain diluent was applied before each perfusion to eliminate possible error. The *p*H of all solutions was within the physiologic range. The same animal preparations also were used for intravenous injection of Premarin. The results, however, were not as decided as with local application over the cortex. Representative electrocorticograms when Premarin is applied over the lesion or injected intravenously appear in Figures 2*a* and 2*b*. Figure 2*a* shows the local effect. A consistent activation of the record obtained with 0.2 to 1% solutions (D and E) consists of increase in spike activity, with subsequent spread to the entire cortex (F) associated with a clinical grand mal seizure. It is interesting that spike phase reversals in C and D originate in symmetrically opposite areas to the lesion, while the site of the lesion seems to maintain a more or less normal activity. This phenomenon has been described by Morrell and Florenz.[21] As can be seen in Figure 2*b*, when a total of 40 mg. of Premarin is injected intravenously (C), the epileptic discharges become activated and spread in both hemispheres, resulting in a clinical generalized seizure (D). Although activation of the focus was observed consistently in 4 other animals tested, precipitation of clinical seizure was observed only this 1 time.

Figures 3*a* and 3*b* illustrate the effect of Premarin on the electrocorticogram of a normal rabbit. In Figure 3*a*, a tendency for an increase in amplitude occurs (E) coincident with the application of a 0.1% solution of Premarin over the normal cortex. Application of 0.2 to 1% solutions results in the appearance of sharp waves and slowing of frequency (F to H). The above changes, although not as decided as in animals with epileptic lesions, were too much outside the basic activity to classify as normal. Figure 3*b* shows the effect of intravenous Premarin on the normal electrocorticogram (A) of a rabbit with an intact cortex. Although some slow potentials appeared, the alterations were of questionable abnormal character.

Observations in epileptic human beings. The spontaneous electroencephalograms of all patients except 1, who had normal tracings, showed focal spikes or other paroxysmal discharges. Clear activation of the abnormality was seen after injection of Premarin in 11 of the 16 patients examined. The activation was characterized by increases in voltage and number of spikes and other paroxysmal discharges per minute of record. These changes became noticeable thirty seconds to twenty-one minutes after injection. The amount of drug given was 20 mg. in 13 patients and 40 mg. in the other 3. Clinical seizures twelve to twenty-four hours after injection were observed in 1 of the 13 patients who received 20 mg. of Premarin intravenously. Of the 3 patients injected intravenously with 40 mg., 1 had a seizure fifteen minutes later and 2 had seizures several hours after injection. The occurrence of seizures hours after injection of Premarin in this small group merely suggests a relationship between injection of estrogens and clinical appearance of seizures.

Some of the results of this study can be seen in Figures 4 to 6*b*. Part A of Figures 4, 5*a*, and 6*a* presents the activity before injection of Premarin; the subsequent parts in each case are taken at various intervals after injection. In Figures 5 and 6, the incidence of paroxysmal elements per minute also is presented in graphic form.

DISCUSSION

The above experimental work suggests a direct convulsive effect of estrogenic substances, particularly in the presence of a preexisting epileptic lesion. This observation is offered as indirect evidence to support our speculations regarding the pathogenesis of catamenial exacerbation of seizures summarized as follows: The estrogenic predominance near the menstrual period, coincidental with aggravation of both seizures and electroencephalographic abnormalities in epileptic women, favors an estrogenic mechanism for the precipitation and spread of the convulsive discharges from a preexisting convulsive focus.

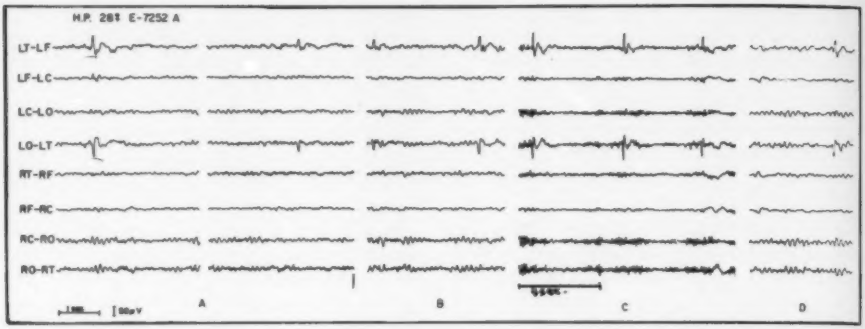

Fig. 5*a*. Activation of spike focus by intravenous injection of Premarin in a patient with psychomotor epilepsy. (A) Basic record showing random spikes in left temporal area. (B and C) Three and ten minutes after 20 mg. of Premarin, the spikes have increased in amplitude and frequency. (D) Thirty minutes after injection, the general voltage of the record is increased, with some decrease in frequency.

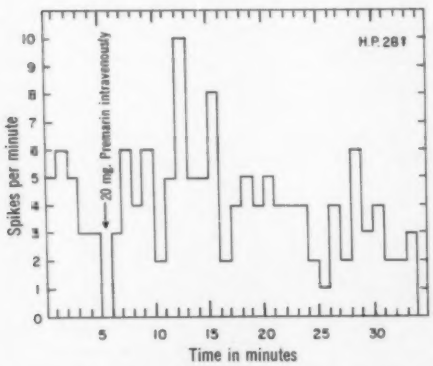

Fig. 5*b*. Graph showing number of spikes per minute after Premarin intravenously. Same patient as in Figure 5*a*

Our findings do not contradict those of Laidlaw,[6] who, as stated earlier, attributed the decrease in seizures at the midluteal period to progesterone and interpreted the menstrual exacerbation of fits as a withdrawal phenomenon due to cessation of progesterone secretion. The results of our study, while not precluding a progesterone anticonvulsive effect at the luteum, strongly suggest that the menstrual exacerbation of seizures are not a progesterone withdrawal phenomenon but a direct estrogenic activating effect.

The mechanism by which estrogens may affect the convulsive focus is obscure. Perhaps, the hormone mediates local biochemical changes involving cell membrane permeability or interferes with acetylcholine metabolism at the site of the epileptic lesion. The latter possibility is favored by Christiansen,[24] who has shown that estrogenic hormones may inhibit cholinesterase activity. This observation is in agreement with the work of Reynolds,[25] who demonstrated an increase in acetylcholine content of denervated transplanted uteri after administration of estrogens.

The results of this study suggest possible therapeutic applications in the control of catamenial exacerbation of seizures. If such seizures are precipitated by increased estrogenic activity during the premenstrual period, administration of hormones having antagonistic properties to estrogens, such as testosterone and progesterone, may help prevent attacks. We have placed 5 of our patients on 10 mg. of progesterone three times a day for four to six days before menstruation. However, the follow-up time of six months in these patients still is too short a period to derive any conclusions. Improvement has been noted in 3 of these patients, but the rest have not had any change.

An additional practical value may be the use of intravenous Premarin for diagnostic activating electroencephalographic studies. From our

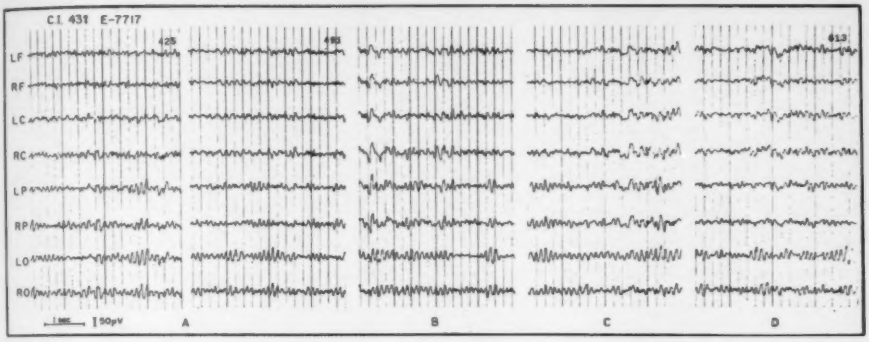

Fig. 6*a*. Activation of electric dysrhythmia by intravenous injection of Premarin in a patient with idiopathic epilepsy. (A) Record before injection shows moderate dysrhythmia. (B and C) Paroxysmal waves four to six per second bilaterally synchronous of twice the basic amplitude during and five minutes after 40 mg. of Premarin. (D) Electric activity returns to pre-injection level twenty minutes after injection.

research, the activating effect apparently is not necessarily limited to patients with catamenial epilepsy.

Because of the possibility of seizures occurring in epileptic patients twelve to twenty-four hours after injection, Premarin should be limited to hospitalized patients until a safe amount of the drug is determined. A study now is under way to estimate the over-all efficacy of Premarin as an activating agent in electroencephalographic studies.

SUMMARY

1] Study of 25 patients with catamenial epilepsy revealed that such seizures occur primarily during the immediate premenstrual and menstrual periods.

2] Study of 6 rabbits revealed a significant epileptogenic effect of estrogens when applied over an irritable cortical lesion produced by ethyl chloride spraying, as well as when injected intravenously in such animals.

3] An activating effect also was observed in the electroencephalograms of 11 of 16 epileptic patients.

4] Possibly, catamenial exacerbation of seizures in epileptic patients is due to increased estrogenic activity during the immediate premenstrual period.

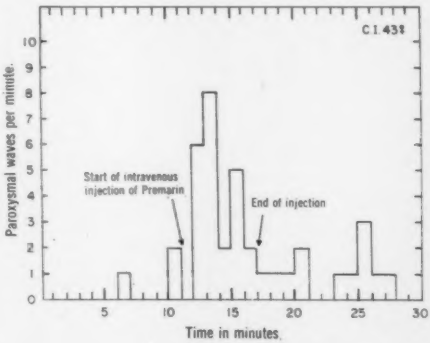

Fig. 6*b*. Graph showing number of paroxysmal waves per minute after Premarin intravenously. Same patient as in Figure 6*a*.

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Cerebellar dysfunction associated with chronic alcoholism

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ALTHOUGH GREENFIELD[1] has stated that no differential diagnosis is possible during life between different forms of cerebellar and spinocerebellar disease, we have recently observed a group of patients whose history, signs, and clinical course are similar enough to set them aside from the mass of these disorders.

During the past three years, 10 patients with cerebellar system disease associated with chronic alcoholism have been observed at Bellevue Hospital. These patients were free of other nervous system diseases which might interfere with a clinical diagnosis of cerebellar disease. The striking features are the long duration of alcoholism prior to onset of symptoms, absence of extreme nutritional deprivation, the much greater involvement of the lower extremities, the improvement with abstinence and hospital care, and the tendency for relapse to occur. No similar disorders had occurred in the family of any patient.

Symptoms of cerebellar system disease in this group were classic—a wide based, reeling gait; decomposition of compound movements of the extremities including dysmetria on point-to-point tests and breakdown of rapid alternating movements; impaired check movements and overactive rebound; and hypoactive deep tendon reflexes. All patients had these signs to varying degrees.

Omitted from this series were patients with signs of dysfunction of the corticospinal tracts, evidence of sensory loss other than minimal impairment of vibration perception in the feet, hereditary tendency to neuromuscular disease, previous trauma associated with the onset of cerebellar symptoms, and evidence on physical examination or laboratory studies of other diseases known to cause central nervous system dysfunction.

MATERIAL

These 10 patients will be described as a group; 2 case histories will be given in detail. Some of the salient features of this group are seen in the accompanying Table 1.

The patients were 33 to 68; average age was 51. All were males. They were Irish, English, Italian, Balkan, and Negro.

The clinical features of this syndrome can be divided conveniently into 3 phases:

1] A prolonged period of severe alcohol addiction occurs during which the patient's diet is maintained at a level which protects him against severe liver disease or evidence of deficiency in mucocutaneous, hematopoietic, gastrointestinal, and peripheral nervous systems.

All the patients admitted prolonged heavy intake of wine, beer, or whiskey. None reported onset of cerebellar symptoms until after five years of alcohol addiction. Adequate diet during most of this period is indicated by the good physical condition of the men. All admitted some degree of prolonged poor nutrition, especially one or two years before onset of symptoms. All but one had the social maladjustments of chronic alcoholism—sporadic unemployment, lack of permanent address, and loss of contact with family and friends. The one exception was homeless on a second admission a year later.

2] The second clinical phase, lasting months to several years, is one of progressive dietary deprivation and increased consumption of alcohol. At some point during this phase, cere-

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This work was supported in part by grant number 2-B-5064, National Institute of Neurological Diseases and Blindness, Department of Health, Education, and Welfare.

TABLE 1

Patient	Age	Years of alcoholism	Duration of symptoms	Previous episodes	Duration of alcoholism to first episode	Remission in hospital
T. Y.	46	20	8 months	0		Marked
R. McK.	38	15	2 years	1	10 years	Marked
J. O'N.	50	30	9 months	0		Marked
H. S.	33	10	2 months	0		Slight
S. G.	68	40	8 months	3	30 years	Marked
G. D.	48	20	2 years	0		Slight
S. C.	65	15	1 month	1	5 years	Marked
J. F.	64	45	1 month	7	30 years	Marked
J. B.	48	25	3 months	1	24 years	Marked
R. Z.	55	40	2 weeks	0	40 years	Slight

bellar symptoms first appear. The patients all complained of walking difficulty two to twenty-four months prior to admisison which was variously described as weakness, falling, or staggering "like I was drunk."

Several had difficulty in coordinating their arms. None had speech difficulty, giddiness, vertigo, blurring of vision, diplopia, paresthesia, or numbness.

3] The final clinical phase seen on admission was associated with rapid deterioration during the several weeks preceding hospitalization with difficulty or inability to walk. Because of increasing inability to walk and loss of revenue, even from odd jobs, most of the men ate virtually nothing immediately prior to admission. They were usually able to continue drinking, although not enough to show the extreme gastrointestinal or mental effects of acute alcohol poisoning.

Of the patients, 5 had previous head injury with concussion, but none had had skull fracture, neurosurgical treatment, or trauma related to cerebellar symptoms.

Although initially showing inanition, all the patients appeared well nourished. Except for several with slight hepatomegaly, none had significant general medical abnormalities. In all patients, neurologic examination initially revealed slight to moderate impairment of highest integrative functions; time orientation was faulty, recent memory defective, and attention span short. The general knowledge and vocabularies of the patients were retained fairly well.

Some generalized weakness was noted in several, which, along with profound ataxia, prevented 4 of the patients from standing. Deep tendon reflexes were either absent or hypoactive. Those patients who could stand swayed in all directions and showed a hesitant, wide-based, reeling gait. All had ataxia of the 4 extremities—decidedly more pronounced in the legs than in the arms.

The limbs were usually symmetrically involved, but sometimes minor differences were found on the 2 sides. Although these patients frequently complained of speaking difficulty, dysarthric speech was found in only 1 patient. True nystagmus was never present; however, initial instability of extreme lateral gaze was often seen.

Laboratory studies were usually unrevealing; 2 patients had mild iron deficiency anemia —due respectively to professional blood donation and a bleeding duodenal ulcer; 4 had minor alterations in liver function studies. Otherwise, the following tests were normal in all patients: complete blood count; urinalysis; stool guaiac; fasting blood sugar; blood urea nitrogen; blood Mazzini; cerebrospinal fluid examination for pressure, appearance, cell count and differential, protein, Wassermann, and colloidal gold; liver function studies including total serum protein and albumin-globulin ratio; cephalin flocculation, total and esterified cholesterol, and alkaline phosphatase; electroencephalogram; and roentgenograms of the chest and skull. Each of 8 patients had normal response to caloric testing.

In 5 patients, pneumoencephalograms were done. In all patients, dilation of the fourth ventricle and appearance of air in dilated sulci over the top of the cerebellum allowed a diagnosis of slight to moderately advanced cerebellar atrophy. Each patient had some dilation of the third and lateral ventricles. On the basis of pneumoencephalograms, the patients in this series cannot be distinguished from those who have generalized ventricular dilation due to diffuse atrophy without cerebellar signs.

The patients were given a diet of 2,500 to 3,000 calories a day containing 95 gm. of protein, 200 to 235 gm. of carbohydrate, and 100 to 130 gm. of fat. A supplement of vitamins was given 3 times a day and contained 1 mg. of thiamine chloride, 2 mg. of riboflavin, 30 mg. of ascorbic acid, 5,000 units of vitamin A, and 1,000 units of vitamin D.

The exact amount of vitamins varied, but all patients improved on the regimen. General strength, mentation, gait, and cerebellar function were better, and nonspecific factors—nutritional lack, exhaustion, exposure, acute intoxication, and effects of withdrawal from alcohol—were improved.

How much the improvement in symptomatology was due to actual improvement in mechanisms directly related to cerebellar functions and how much was due to improved physical and psychologic ability to compensate for defective cerebellar mechanisms is impossible to say. The only patients not showing early rapid improvement were the 2 who had a good diet and abstinence in other institutions several weeks prior to hospitalization.

Following the first week of rapid improvement shown by 7 of the 10 patients, no further improvement was observed for varying periods. In none did evidence of cerebellar disease clear completely—even in those patients followed for two years. However, the disability usually became difficult to detect.

Prominent among the characteristics of this syndrome is the tendency to relapse. Of our patients, 5 had had a total of 13 previous episodes of staggering gait which required hospitalization. Each episode was marked by improvement in the hospital and exacerbation at some later time associated with increased consumption of alcohol and decreased consumption of food.

CASE REPORTS

Case 1. A 48-year-old, divorced, unemployed man complained that for six to eight months he had noticed increased symptoms of staggering, "as if I were drunk."

The patient had been a heavy drinker for at least twenty years, particularly in the previous three or four years. His diet was irregular and inadequate.

During the six weeks prior to hospitalization, he lived at a home for indigent men. At this time, his symptoms remained stable. He denied all other symptoms referable to the nervous system. The patient had had gastrointestinal bleeding and subtotal gastric resection two years before. At the time of operation, the patient was ambulatory and routine examination revealed no neurologic abnormalities.

Initial physical examination was normal; the patient was well nourished, well developed, and not in acute distress. No evidence of deficiency disease or liver disease was found.

The patient was well oriented but had difficulty with recent memory, calculation, and recall. He was unable to stand with his feet together and swayed in all directions. His gait was hesitant, wide based, and reeling, and step movements were irregular.

All cranial functions were normal, including eye movements and speech. He had mild terminal dysmetria on point-to-point testing of the arms. Rapid rhythmic alternating movements, resistance to passive stretch, check movements, rebound, power, and sensation were normal. The biceps, triceps, and radial reflexes were all present but hypoactive. Motility and sensory perception were normal over the thorax and abdomen.

His legs showed gross dysmetria and decomposition of movements on point-to-point test. Check was impaired, and severe rebound was present. Rapid alternating movements were extremely impaired. Resistance to passive stretch, power, and perception of all sensory modalities except vibration were intact. Threshold for vibration perception in the feet was slightly increased. Deep tendon reflexes were all absent. Plantar responses were flexor.

Laboratory studies showed a mild hypochromic, microcytic anemia which responded to oral iron therapy. Other laboratory studies were normal.

During a six-week period on high protein diet and vitamin supplements, the patient steadily improved. At the end of this time, he had no difficulty ambulating, but his gait was slightly wide-based. Arm function was not abnormal, and only a very slight terminal dysmetria on point-to-point tests could be elicited in his legs. In his feet, the slight decrease in perception of vibration remained unchanged. After no further change in the sixth to eighth weeks of hospitalization, the patient was discharged.

Case 2. A 48-year-old white janitor who had three months' progressive weakness in his legs was admitted to the hospital.

The patient had been drinking heavily for twenty-five years. However, he had been in good health until three years before admission when he began to drink more heavily and gave up most of his responsibilities. His diet became progressively worse. Approximately three months prior to admission, the patient noticed progressive walking difficulty. For several weeks he had been confined to bed, eating very little but continuing to drink wine.

Physical examination showed a well developed, well nourished patient who was in no distress. The liver edge was smooth and nontender, and palpable two fingerbreadths below the right costal margin. Cutaneous and mucous membrane deficiency lesions were absent.

Neurologic examination showed that the patient was well oriented and cooperative. He had a short attention span, poor insight and calculation, and rather meager general information and vocabulary. His gait was hesitant, wide-based, and reeling, and step movements were irregular. He had no nystagmus or dysarthria. His arms had slight terminal dysmetria on point-to-point testing; rapid alternating movements, check and rebound, resistance to passive stretch, power, and sensory perception were normal. Deep tendon reflexes were absent. Examination of the trunk was unremarkable; superficial abdominal reflexes and cremasteric reflexes were symmetrically active. His legs showed extreme dysmetria on point-to-point tests, impaired check and rebound, and impaired rapid alternating movements. Resistance to passive stretch and power and all modalities of sensation was normal. No deep tendon reflexes could be elicited. Plantar responses were flexor.

Laboratory studies were within normal limits.

On a high protein diet and vitamin supplements, the patient improved dramatically within a few days. His mentation was better, and he became fully ambulatory. His cerebellar signs continued to improve slowly during the next two weeks. On discharge, a slightly wide-based gait was the only evidence of cerebellar dysfunction.

The patient returned thirteen months later complaining of walking difficulty. He said he had done well after leaving the hospital, except for slight unsteadiness on his legs. However, he did not continue vitamin supplements, his drinking increased, and his diet became progressively worse. Approximately two months before his second hospitalization, he began to stagger. For approximately one month, he had been completely unable to walk and had eaten little. Again he denied all other symptoms.

Physical and neurologic examinations were almost identical to those of first admission, except that this time the patient was unable to stand without aid and the cerebellar signs were more noticeable in both arms and legs. Again cerebellar dysfunction and loss of deep tendon reflexes were the only abnormal signs.

Laboratory studies were unremarkable.

The patient was given a high protein diet and vitamin supplements and was able to walk after the first week. His cerebellar dysfunction slowly disappeared and remained almost stable during his last two weeks in the hospital. At the time of discharge, no signs of cerebellar dysfunction were found in his arms and only a slight terminal unsteadiness on point-to-point testing occurred in his legs. These findings were similar to those on previous discharge.

DISCUSSION

Since acute alcoholism produces symptoms resembling cerebellar dysfunction, chronic alcoholism may cause lasting cerebellar damage. The use of alcohol to bring out cerebellar dysfunction has also been described.[2] The precise relationship, however, between chronic alcoholism and cerebellar degeneration of late onset is more difficult to delineate.

Pathologic studies of this relationship are rare. In 1905, Thomas[3] reported *atrophie lamellaire des cellules de Purkinje* in a woman with chronic alcoholism. In 1922, Marie, Foix, and Alajouanine[4] brought together varied cases of nonfamilial cerebellar ataxia with cortical degeneration; they mentioned alcoholism as a possible cause but presented no new cases. Stender and Lüthy[5] reported the pathologic findings of cerebellar atrophy—primarily Purkinje cells—in a man with longstanding alcoholism, seizures, and at least 3 episodes of delirium tremens.

Parker and Kernohan[6,7] later reviewed all the cases of parenchymatous cortical cerebellar atrophy and presented new observations of their own. They mentioned these earlier occurrences in conjunction with alcoholism but tended to view a viral etiology as more likely, at least for a portion of the group.

In 1935, Lhermitte[8] reported on 5 further patients, 1 a man who had been a heavy drinker. DeHaene[9] reported the pathologic findings of cortical cerebellar degeneration in a patient with a forty-year history of high ethanol intake. More recently, Zulch[10,11] has reviewed the clinical and pathologic findings in 39 patients with cortical cerebellar atrophy, 5 of whom were alcoholics. Of the relatively few pathologically proved cases of cortical cerebellar degeneration in the literature, alco-

holism has been prominently implicated in the pathogenesis.

In the past twenty years, a number of patients with cerebellar ataxia and chronic alcoholism have been recorded. In 1940, Romano, Michael, and Merritt[12] reported 5 men with cerebellar ataxia that predominantly involved the lower extremities; onset occurred after 30, and all were addicted to prolonged and excessive use of alcohol. None had deficiency disease or peripheral neuropathy.

Skillicorn[13] has reported that 5 of 6 similar patients had, in addition, evidence of organic mental change; peripheral neuropathy occurred in 3. Air studies in all 6 revealed large ventricles and small cerebellums.

Chodoff and associates[14] have reported 16 similar patients.

In animals, administration of alcohol produces degenerative changes of the Purkinje layer.[15]

Victor, Adams, and Mancall[16] reported their findings in 35 patients with cerebellar ataxia who drank excessively and had malnutrition. All had gait disturbance and incoordination of the legs, although speech and arms were relatively uninvolved. Autopsy was performed in 4, and primary cortical cerebellar degeneration, especially in the anterior and superior parts of the vermis and hemispheres, was noted. Apparently, a clear relationship exists between cerebellar ataxia and alcoholism.

The patients in the present series had remission of symptoms while on an adequate diet in the hospital. These symptoms returned when excessive use of alcohol and poor dietary habits were resumed.

In the previous series, the tendency has been for slow progression of symptoms. Previous remissions and exacerbations suggest multiple sclerosis or a condition akin to Wernicke's encephalopathy. In no patient, however, has significant asymmetry of signs or evidence of dissemination appeared, as would be expected in multiple sclerosis. The peripheral neuropathy, extraocular abnormalities, and severe mental signs of Wernicke's disease do not appear.

Marie, Foix, and Alajouanine[4] stated that none of the patients reported to that time had improved; rather, the course of these patients was steadily downhill. Stender and Lüthy[5] noted that, after a stormy onset, peripheral neuropathy improved in their patient.

Zulch[11] mentioned that function might remain partially compromised or show some return, but he did not elaborate.

In none of the patients reported by Romano and associates,[12] Skillicorn,[13] or Chodoff and associates[14] was any significant improvement in ataxia noted.

For their 35 patients, Victor, Adams, and Mancall[16] report that "progression of cerebellar symptoms was associated with continued excessive drinking and conversely stabilization was associated with abstinence and improved nutrition." None of these patients improved. Thus, the striking improvement noted in the present series is apparently quite unusual. The relationship between the improvement in these patients and the administration of high-calorie high-protein diets and vitamin supplements is not clear. The absence of other evidence of general or specific vitamin deficiencies suggests that cerebellar symptoms are not related to these factors. The relationship of abstinence to either improvement or stabilization of symptoms suggests that the toxic effects of alcohol may be the most important cause of cerebellar deficits.

That clinical improvement occurs in other cerebellar disorders is well known—as has been shown in the acute cerebellar ataxias of childhood,[17,20] renal aminoaciduria,[21] and Wernicke's encephalopathy. None of these diseases would appear implicated in the present series, although the pathophysiology may be similar.

SUMMARY

1] A study has been made of 10 patients with cerebellar dysfunction and chronic alcoholism without other evidence of nutritional deficiency.

2] Evidence of cerebellar dysfunction was most apparent in the legs and slight or absent in the trunk and arms.

3] All the patients steadily improved in the hospital when given adequate diets and supplementary protein and vitamins.

4] The majority were discharged from the hospital with insignificant or no evidence of cerebellar dysfunction.

5] A tendency for relapse is noted among patients who resumed excessive use of alcohol intake and had inadequate diet.

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Quantitative histochemistry of brain tumors and analogous normal tissue

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THE BIOCHEMICAL STUDY of brain tumors has been difficult because of the lack of histologic homogeneity of tumor tissue. This lack of homogeneity is the result not merely of variation in neoplastic cell population, but also of normal brain components passing through the tumor, increased vascularity, focal necrosis, and cyst formation. Such diversity in the structure of tumors makes biochemical analysis difficult because of a high degree of scatter in the results.[1,2] However, Lowry's[3] modifications and refinements of Linderstrøm-Lang's general histochemical technics have made the examination of complex tissue feasible.

Using the microscope for direct dissection of lyophilized sections of tumors allows the removal of 0.1 to 0.3 μg. sections composed predominantly of neoplastic cells; extraneous tissue is avoided. Normal brain tissue may be dissected in the same manner, and comparison tissues are obtained which may be looked upon as normal counterparts of the tumors. With this technic, differences in biochemical findings should be those inherent in the neoplastic cells and not the result of random amounts of cellular contaminants.

This study presents a comparison of some aspects of cellular glucose metabolism in normal cerebral tissues and in neoplastic tissues. Each of 4 enzymes concerned with a different aspect of glucose metabolism was investigated. These enzymes were measured in 4 human brain tumors and in normal astrocytes, ependymal cells, and dura mater from the brains of healthy, adult Macaca mulatta monkeys. Analyses of normal glial elements in correlation with studies of normal brain metabolism are urgently needed.

MATERIAL AND METHODS

Analysis was made of 4 human brain tumors—a glioblastoma, an astrocytoma grade II, an ependymoma, and a psammomatous meningioma. These tumors were obtained through the courtesy of Dr. Henry Schwartz and members of his staff. Pathologic classification of the tumors was made by Dr. David E. Smith. Immediately after removal, tissue blocks were cut from areas of the tumor. These tumor blocks were frozen by immersion in liquid nitrogen, sectioned, dehydrated, and stored by methods previously described.[3] The dehydrated sections were dissected freehand under a dissecting microscope where white matter, gray matter, and areas of high vascularity and of necrosis were easily identified.

Considerable variation may occur in the cell population density which cannot be seen under the microscope in an unstained section. This variation was controlled by thionine staining[4] of every sixth to eight section cut from the tissue block and frequent staining of the lyophilized sections. Only pieces of uniformly high cellularity were selected by microscope dissection. The dissected tissues were 0.1 to 0.4 μg. in size and were composed of neoplastic cells. Removing pieces of tissue larger than 1 μg. from the sections of many of the tumors is difficult without including nonneoplastic or necrotic tissues. Unless this dissection was performed, variation in cellularity of the tumor tissues and inclusion of nontumor tissues introduced wide variations in enzymatic activity.

The normal tissues were removed from adult monkeys—the dura mater of the longitudinal sinus, ependyma of the lateral ventricle, and astrocytes from the wings of the area postrema[5]—and were prepared in the same fashion as the brain tumors. The ependyma and subependymal cerebral tissues were removed in

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TABLE 1
CONDITIONS OF REACTION

	Incubation volume	*pH*	*Buffer*	*Substrate*	*Coenzyme*	*Standard*
Malic dehydrogenase	20 μl.	8.7	0.1 M. tris	Oxaloacetic acid 2 mM.	DPNH 2 mM.	Malic acid
Lactic dehydrogenase*	10 μl.	7.74	0.1 M. tris	Pyruvic acid 2 mM.	DPNH 2 mM.	DPN
Phosphohexoisomerase	3 μl.	7.98	0.1 M. tris	G-6-P 90 mM.	—	Fructose
Glucose-6-phosphate dehydrogenase†	5 μl.	9.5	0.1 M. AMP_2	G-6-P 4 mM.	TPN 0.15 mM.	TPNH

*20 mM. nicotinamide used to suppress DPNase
†0.5 mM. $MgCl_2$
0.4 mM. Na versenate
AMP_2 is 2-Amino-2-Methyl-1,3-propanediol (Eastman Kodak Company)
Tris is tris (hydroxymethyl) aminomethane (Sigma 7-9) Sigma Chemical Company, St. Louis.

strips by sharp dissection. The strips were then rolled with the ependyma on the inside and the subependymal tissues on the outside. Rolling of the ependyma was found to be necessary in its preparation, since freezing and handling of unrolled ependymal tissue partially destroys it. The astrocytes were obtained from the area postrema, an area of pure pleomorphic astrocytes[6] at the obex of the fourth ventricle. The pleomorphism is most marked in the body of the area postrema and was therefore avoided. All sections were dissected from the area's wings. The ependyma of the fourth ventricle was dissected off the area postrema prior to removal of astrocyte sections, thus avoiding ependymal contamination. This ependyma was not used for enzymatic determination. The dura mater sections were from the region of the longitudinal sinus. During dural dissection, blood in the longitudinal sinus and dural veins was carefully avoided.

Chemical methods. Enzymes studied were: phosphohexoisomerase and lactic dehydrogenase of the Meyerhof-Emden cycle, malic dehydrogenase of the citric acid cycle, and glucose-6-phosphate dehydrogenase of the glucose-6-phosphate shunt. The activity of each enzyme was measured under optimal conditions. The enzyme incubation time was thirty minutes at 38° C., and activity was expressed in mols of product formed per kilo of dry tissue per hour. Methods for handling these small volumes and section weights have been described.[7] Each assay was accompanied by control measurements with fresh rabbit-brain homogenate. The homogenate consisted of whole rabbit brain rostral to the superior colliculi homogenized in the Waring blender with redistilled water. Homogenate dilutions of greater than 1 to 200 were protected by the presence of .05% crystalline bovine albumin. Conditions of reaction are seen in Table 1.

TABLE 2
QUANTITATIVE HISTOCHEMICAL DATA ON G-6PH, LDH, MDH, PHOSPHOHEXOISOMERASE

	Malic dehydrogenase	*Lactic dehydrogenase*	*Phosphohexoisomerase*	*Glucose-6-phosphate dehydrogenase*
Brain homogenate	192	35	103	0.77
Astrocytes	103 ± 3.	34 ± 4.	31 ± 1.3	0.52 ± .04
Astrocytoma grade II	32 ± 3.	37 ± 4.	56 ± 4.	2.0 ± .2
Glioblastoma	114 ± 4.	63 ± 2.	104 ± 1.	1.6 ± .2
Ependyma	110 ± 4.	47 ± 4.	101 ± 4.	0.71 ± .04
Ependymoma	31 ± 5.	68 ± 8.	43 ± 2.	2.3 ± .2
Dura mater	4.5 ± .3	2.9 ± .3	3.2 ± .3	0.23 ± .01
Psammomatous meningioma	38 ± 0.3	51 ± 2.	57 ± 2.	2.6 ± .1

Values are expressed as mols of substrate converted per kilo dry weight per hour
The standard errors are indicated

Phosphohexoisomerase activity was measured by the rate of fructose-6-phosphate formation from glucose-6-phosphate. This method has been described.[8] Malic dehydrogenase was measured by the rate of conversion of oxaloacetate to malate. Oxaloacetate in solution is unstable at room temperature and must be freshly prepared for each run. The malate formed was measured by a previously described method.[9] Glucose-6-phosphate dehydrogenase was measured by the rate of triphosphopyridine nucleotide (TPNH) production from TPN^+ and glucose-6-phosphate.[10] The sensitivity of the measurement was increased by oxidizing the formed TPNH and reading fluorescence produced from TPN^+, (sensitivity 10^{-8} mols per liter). This was done by stopping the reaction and destroying the substrate TPN^+ by one-hour incubation at 38° C. in 0.02 NaOH. Oxidation of the formed TPNH and production of fluorescence was accomplished by one-hour incubation at 38° C. in 0.02% H_2O_2 in 6.6N NaOH.[11] Fluorescence of TPN^+ was measured in the same way as diphosphopyridine nucleotide (DPN^+). Lactic dehydrogenase was measured with pyruvate plus DPNH, and the activity was assessed by the DPN formed.[8]

RESULTS

Comparison of homogenate and nervous system supporting tissues. (Table 2) The enzymatic activity of astrocytes when compared with homogenates is markedly lower for malic dehydrogenase and phosphohexoisomerase, moderately lower for glucose-6-phosphate dehydrogenase, and the same for lactic dehydrogenase. The homogenate activity is an average of the activity of neurons, glial elements, and myelin sheaths. Presumably, neurons, as a whole, have a higher metabolism than that indicated by brain homogenates. Therefore, a comparison of astrocytes, the chief supporting element of the nervous system, with a homogenate does not directly indicate the wide magnitude of difference that may exist between the metabolism of astrocytes and neurons. When compared to a homogenate, 3 enzyme activities of astrocytes are moderately low but, possibly, compared to neurons, the activities would be strikingly low. The enzymatic activities in ependyma are of the same magnitude as those in astrocytes with the marked exception of phosphohexoisomerase which is three times greater than in astrocytes. The activities of all enzymes in dura mater are very low in comparison with the enzymatic activity of homogenate and the other tissues studied. This low activity is not unexpected and is probably a reflection of high-collagen and fiber content, and the associated low cellularity.

Comparison of tumors with precursor tissues. (Table 2) The astrocytoma and ependymoma show a fall in the malic dehydrogenase activity to a level of activity which is 30% of that in astrocytes and ependyma. This might suggest a marked reduction in the activity of the citric acid cycle. The glucose-6-phosphate dehydrogenase activity is threefold to fourfold greater in the astrocytoma and the ependymoma as compared to the astrocytes and ependyma. Apparently, activity of glucose-6-phosphate shunt is markedly increased in both.

The consistent changes found in the enzymes of the citric acid cycle and glucose-6-phosphate shunt mechanism do not occur in the 2 enzymes of the glycolytic cycle of astrocytoma and ependymoma. Also, the parallelism in the direction of change anticipated in these 2 enzymes of the same cycle was not found. The phosphohexoisomerase activity in the astrocytoma was twice that of the astrocytes, while the phosphohexoisomerase activity of the ependymoma was only 50% of that in ependyma.

The activities of all of the enzymes in the meningioma are 10 to 20 times greater than that of dura mater. This high activity in meningioma most probably reflects the great cellularity and low collagen content of the tumor as compared to the histologic picture of low cellularity and high collagen in the dura mater. If the activities of the enzymes in the dura mater were expressed in collagen-free dry weight rather than total dry weight, the great difference in enzymatic activity of meningioma and dura mater could be expected to be less striking.

Of the enzymatic activities measured in glioblastoma, 2 are considerably higher than those of any other tumors. Lactic dehydrogenase activity equals that of the ependymoma, and glucose-6-phosphate dehydrogenase activity is 60 to 80% as high as in the other 3 tumors.

However, the glioblastoma glucose-6-phosphate dehydrogenase activity is from 2 to 7 times greater than that of the homogenate or normal tissues.

DISCUSSION

The application of quantitative histochemical methods to the study of brain tumor yields consistent and reproducible quantitative results. In order to obtain such results, analysis must be made of tumor areas that maintain a uniform, pure, neoplastic-cell population and are free of necrosis, blood vessels, and normal cerebral tissues. Tissues of this purity may be obtained by freehand dissection under direct microscopic visualization of lyophilized tissues. Sections of this purity will frequently have to be smaller than .001 cc. (1 μg.) and in this study were .0001 cc. to .0004 cc. (0.1 to 0.4 μg.). Equipment and methods of high sensitivity have been developed for biochemical analyses of tissue of this volume. These methods would seem to have wide application to the study of tumors in other body organs.

Glucose-6-phosphate dehydrogenase was the only enzyme measured that showed a consistent direction of change in activity in all of the tumors studied. This enzyme was 3 to 10 times higher in all tumors than in homogenate or normal tissues. The 3 other enzymes showed considerable difference of activity in tumors and in normal tissues. However, none of these differences were consistently in the same direction. For example, malic dehydrogenase was high in glioblastoma and low in astrocytoma and ependymoma. These findings would seem to indicate that the glucose-6-phosphate shunt is very active in all of these tumors—irrespective of its histologic classification—while anaerobic glycolysis and, possibly, the citric acid cycle metabolism are differently affected in each of the histologic types. However, other workers[12] studying normal mammalian tissue and extracerebral tumors found an increase in anaerobic glycolysis of all of the tumors.

Only 1 tumor of each type has been analyzed. Because of the wide variation among tumors of the same class, a much larger series of tumors must be analyzed before generalizations can be made. Also, the number of enzymes measured in these tumors must be greatly increased in order to assess more truly the metabolic pattern. One of the most difficult and pressing problems in the study of the normal brain is to evaluate the respective contributions of neurons and glial elements to the total brain metabolism. Present analyses of astrocytes are a contribution to this problem.

SUMMARY

1] Quantitative histochemical methods were utilized in the study of 4 brain tumors and their analogous tissues.

2] The activity of lactic dehydrogenase, malic dehydrogenase, phosphohexoisomerase, and glucose-6-phosphate dehydrogenase were measured in 4 brain tumors—a glioblastoma, an astrocytoma, an ependymoma, and a psammomatous meningioma—and in normal astrocytes, normal ependyma, and the dura mater.

3] The enzymatic activity of astrocytes was found to be lower than that of central nervous system neuronal tissues.

4] The activity of glucose-6-phosphate dehydrogenase was found to be 3 to 10 times greater in all tumors, irrespective of histologic type, as compared with the analogous normal tissue.

The author wishes to express his gratitude to Dr. Eli Robin, Dr. Oliver Lowry, Dr. Henry G. Schwartz, and Mrs. Nira Roberts for their kind advice and assistance.

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CASE REPORT

Eosinophilia of the cerebrospinal fluid of noninfectious origin

Report of 2 cases

Laibe A. Kessler, M.D., and William R. Cheek, M.D.

"EOSINOPHILIA OF THE spinal fluid is practically pathognomonic of parasitic disease of the nervous system." This quotation from Wechsler's *Textbook of Neurology* is a generally accepted tenet of neurology.[1–5]

A review of the literature calls attention to other possible causes of spinal fluid eosinophilia. In 1907, Mosny and Harvier[6] described its occurrence in neurosyphilis with no concurrent blood eosinophilia. Wolff[7] recently reported a case of unexplained eosinophilic meningitis which he thought was caused by a new type of paint spray. Carroll and associates[8] observed eosinophilia in the spinal fluid following intrathecal injection of horse serum in the treatment of dementia praecox. Several cases of spinal fluid eosinophilia appear in which no explanations are proffered.[9,10]

We have observed 2 patients with marked eosinophilia of the spinal fluid in whom no evidence of parasitic disease could be demonstrated. Both these patients had intracranial shunting procedures in which standard rubber catheters were used. We believe that the spinal fluid eosinophilia in these patients may have been caused by a sensitivity reaction to the rubber catheter. To our knowledge, this has not been previously reported.

CASE REPORTS

Case 1. A 14-year-old girl was admitted to the Neurological Institute of New York with intermittent headaches. For two years, she had had seizures. In 5 or 6 of these seizures, the patient lost contact without having aura, walked aimlessly, and slept two to three hours postictally; she had complete amnesia for the seizure. Headaches occurred daily for two months prior to admission.

On admission, examination revealed extreme myopia in the left eye but no papilledema. The remainder of the physical and neurologic examination was normal.

Skull roentgenograms showed a thinned sella and destruction of the posterior clinoids. The electroencephalogram had an occasional atypical spike and wave pattern bilaterally.

Routine blood and urine studies were normal: white blood corpuscles, 12,800 per cubic millimeter, with 57% neutrophils, 36% lymphocytes, and 6% eosinophils. The sedimentation rate was 8 mm. per hour. Serology was negative. Serum sodium was 137.7 mEq. per liter; serum potassium, 4.2 mEq. per liter. Basal metabolism rate was —19%.

Shortly after admission, a spinal tap was performed which revealed a pressure of 270 mm. of spinal fluid; protein, 31 mg. per cent; sugar, 59 mg. per cent; and 1 white blood corpuscle. Because of the increased pressure, a ventriculogram was performed which showed symmetric dilation of the lateral and third ventricles; no air passed into the aqueduct of Sylvius. Aqueductal stenosis was diagnosed, and a ventriculocisternostomy was performed with a rubber catheter.

Postoperatively, the patient did well except for a spiking type of fever between 100 and 102° F. Physical examination was negative. Chest roentgenograms were normal, and spinal taps on the second, fourth, and seventh days showed a decreasing cell count with quite normal sugar values (see table, Case 1). The cerebrospinal fluid, blood, sputum, and urine cultures were negative.

On the twelfth postoperative day, the patient had slight swelling of both wrist joints. Penicillin and streptomycin were discontinued and an antihistamine administered.

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SPINAL FLUID REPORTS

Days after operation*	Red blood cells per mm.³	White blood cells per mm.³	Polymorphonuclear cells %	Lymphocytes %	Eosinophils %	Sugar mg.%	Protein mg.%
			Case 1				
— 4	0	1				59	31
ov	285	1					11
+ 2	11,000	1,750	84	16		50	
+ 4	3,550	200	76	24		59	76
+ 7	625	44	15	85		58	75
+15	160	13	7	6		90	72
+30	0	440		20	80		159
+34	0	365		10	90	35	159
+37	0	376		8	92	36	178
			Case 2				
0	346	2					13
+ 9	1,150	140	60	35		62	288
+20		276	30	70		34	144
+21		720	85	15		37	125
+23	100	650				42	170
+27		310	15	85		42	210
+34	56r	212	68	32		41	169
+41		60		50	50	50	152
+52		162	5	31	61	36	372
+55		120	8	42	50	48	245
+61		112		8	90	48	245
+77		70		35	63	46	155
Second admission:							
5 months + 17	0	0	0	0	0	72	68
6 months + 1	0	1	0	0	0		

*Days related to insertion of rubber catheter
v = ventricular fluid r = fresh o = operative day

By the fourteenth postoperative day, fever persisted but, again, cultures of the blood, nose, throat, spinal fluid, and urine showed no growth. Chest roentgenograms, electrocardiogram, and antistreptolysin titers were also normal, as were leukocyte and differential blood counts. The cerebrospinal fluid now showed only 13 white blood corpuscles with 7 neutrophils and 6 lymphocytes, while the cerebrospinal fluid sugar was 90 mg. per cent and total protein, 72 mg. per cent.

Because of continued and unexplained fever, another spinal tap was done on the thirtieth postoperative day. This revealed 440 white blood corpuscles with 80% eosinophils, and the peripheral blood smear now showed an eosinophilia of 12% with a total of 7,000 white blood corpuscles per cubic millimeter. The cerebrospinal fluid revealed 365 white cells with 90% eosinophilia four days later (see table).

Prior to this eosinophilia, the patient had been given Chlor-Trimeton without results. Therefore, 20 mg. of Metacortin was administered daily. After three days, another tap revealed the same cerebrospinal fluid findings as before, while the peripheral blood smear showed 18% eosinophilia. Metacortin was discontinued.

Meanwhile, the following tests had all proved negative: Trichinella skin test, Echinococcus complement fixation test, cerebrospinal fluid cultures for fungi, and stool and sputum examinations for ova and parasites.

The patient was finally discharged with a diagnosis of aqueductal stenosis of unknown etiology and eosinophilia probably attributable to sensitivity to the rubber tube.

Except for 1 seizure, the patient has been asymptomatic for a year.

Case 2. A 7-year-old boy was admitted to Babies Hospital on February 5, 1957, with dizziness of eight months' duration. He had had occipital headaches daily for a month. His parents said that vision was blurred in his right eye and his gait was unsteady and he had had excessive salivation and tilting of his head to the right for ten days.

On examination, the patient held his head tilted to the left and walked with an ataxic gait. He had bilateral early papilledema, nystagmus on right and left lateral gaze, and poor convergence. Slight left fourth and left seventh cranial nerve palsies and bilateral reduction of the gag reflexes were also seen. Finger-to-nose and heel-to-knee

testing showed ataxia in all 4 extremities. Laboratory data revealed 6,050 white blood corpuscles per cubic millimeter; neutrophils, 37%; lymphocytes, 56%; monocytes, 4%; and eosinophils, 3%. Urinalysis was normal.

Course. On February 8, 1957, ventriculography revealed a large pons and obstruction of the aqueduct of Sylvius. At suboccipital craniectomy, diagnosis of brain stem glioma was confirmed. A rubber catheter was inserted through the aqueduct into the third ventricle from the cisterna magna, and a tracheotomy was done postoperatively.

By the ninth postoperative day, the patient was alert and oriented; he had no disabilities except left medial rectus palsy and mild left hemiparesis. Because his temperature had been 100.5 to 104° since operation, a lumbar puncture was done which revealed an initial cerebrospinal fluid pressure of 250 mm.; total protein, 288 mg. per cent; sugar, 62 mg. per cent; 1,150 crenated red blood corpuscles per cubic millimeter; 140 white blood corpuscles per cubic millimeter with 60% neutrophils, 35% lymphocytes, and 5% monocytes; and a positive culture for Staphylococcus aureus. Multiple subsequent cultures were negative. Antibiotics were administered because of the positive culture.

The patient remained the same until the twentieth postoperative day when the craniectomy site bulged. Because of this and the persistence of fever, spinal taps were repeated frequently until discharge (see table, Case 2). White cell counts remained moderately elevated, but percentage of polymorphonuclear cells decreased. On the forty-first postoperative day, the cell count had fallen to the lowest postoperative level (60 white blood cells per cubic millimeter) but a 50% eosinophilia was reported. As the table shows, this increased to 90% on the sixty-first day. Cerebrospinal fluid sugars were within normal range. Remaining cultures were repeatedly negative.

During this period, the patient received roentgen therapy. Increased intracranial pressure gradually subsided, and all antibiotics were stopped on the sixty-fourth postoperative day. By April 21, temperature was normal. He was discharged on April 27.

While in the hospital, the patient was administered the following antibiotics: penicillin, triple sulfonamides, Achromycin, tetracycline, Albamycin, erythromycin, and streptomycin.

Following the development of cerebrospinal fluid eosinophilia, stool examinations for ova and parasites, sputum and blood cultures for parasites, spinal fluid examination for fungi, and Trichinella and Echinococcus complement fixation tests all proved negative.

Multiple peripheral blood counts were recorded with eosinophils ranging from 3% on admission to 8% two days before discharge. With the exception of initial postoperative leukocytosis, the counts were otherwise normal.

The patient was readmitted to the Babies Hospital on July 24 after six days of vomiting, headache, dysarthria, and increasing left hemiparesis.

Radiotherapy was begun July 29. Lumbar punctures at this time were essentially normal. However, he became progressively more unresponsive and died on August 21. Permission for autopsy was refused.

COMMENTS

In both these patients, repeated spinal taps were performed because of continued fever and prolonged, increased intracranial pressure. Obviously, the spinal fluid abnormalities present immediately after surgery gradually regressed except for eosinophilia, which heralded a new and apparently isolated event. Eosinophilia was first observed on the thirtieth postoperative day in Case 1 and on the forty-first postoperative day in Case 2. At this time, neither patient had evidence of exacerbation of illness; both had improved after operation.

While central nervous system infection was a possible explanation for the eosinophilia, there was considerable evidence against it. Neither had been away from the northeastern part of the United States. Trichinosis seemed unlikely in the absence of gastrointestinal symptoms and muscle pain and the negative Trichinella skin tests. The absence of Schistosoma ova in the stools apparently ruled out schistosomiasis. Cysticercosis, rare in the United States, usually occurs in the posterior fossa and was not found in either patient. The absence of ova or larvae in the stool or sputum eliminated Paragonimus westermani and Ascaris as etiologic possibilities. In both patients, the Echinococcus complement fixation test was negative.

A positive culture for Staphylococcus was obtained in Case 2 but could have been a contaminant. At the time, cerebrospinal fluid sugar was 60 mg. per cent. Although not benefited by antibiotics, both patients did well. Both were seen after protracted periods—five months and one year, respectively—without signs of infection. These facts seem to preclude infectious etiology of the eosinophilia.

Evidence indicates both the children were predisposed to sensitization. The first patient had swollen joints early in the postoperative period—probably from penicillin. The second patient was reported to have had an episode of joint swelling two years before which was tentatively diagnosed as rheumatic fever. In

both, blood eosinophilia accompanied the spinal fluid reaction, although to a lesser degree.

SUMMARY

Standard rubber catheters were used for intracranial shunts in 2 patients. Eosinophilia of the spinal fluid occurred thirty and forty-one days after operation—long after expected postoperative spinal fluid changes usually disappear. In neither patient could a diagnosis of parasitic disease or other infection be established.

We feel it is possible that use of intracerebral rubber catheters can cause an allergic reaction within the central nervous system in some patients and may account for fever and spinal fluid eosinophilia in the postoperative period.

ACKNOWLEDGMENT

The authors wish to thank Dr. J. Lawrence Pool for his advice and helpful criticism.

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NAME CHANGE AT WARNER-CHILCOTT

The Laboratory Supply Division of Warner-Chilcott Laboratories, Morris Plains, N. J., has changed its name to General Diagnostics Division, announced Dr. Leonard A. Scheele, president of the company.

Division manager Raphael Cohen stated that the division's major concern will be to help the clinical laboratory establish accuracy and precision in testing by making available diagnostic reagents and testing methods which simplify and strengthen these procedures.

Representatives of the division work directly with diagnostic centers throughout the country. They help the centers solve technical problems and introduce new diagnostic reagents developed by Warner-Chilcott scientists.

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NEW HAITI PSYCHIATRIC CENTER

The first shipment of drugs, consisting of 10,000 Equanil tablets (Wyeth Laboratories, Radnor, Pennsylvania), has been sent to a new psychiatric center in Haiti. Funds for construction and for necessary pharmaceuticals are being furnished by 3 American firms: Hoffmann-La-Roche, Inc., Nutley, New Jersey, Schering Corporation, Bloomfield, New Jersey and Wyeth International, Ltd., Radnor, Pennsylvania.

The program is being conducted under the auspices of MEDICO (Medical International Cooperation), the Haitian government, and the Department of Mental Hygiene of the State of New York. Dr. Louis Mars, noted psychiatrist and Haitian Minister of Foreign Affairs, is directing the project. Dr. Nathan Kline, director of research, Rockland State Hospital, Orangeburg, New York, is consultant.

NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

Francis M. Forster, President
Augustus S. Rose, President-Elect
A. L. Sahs, Vice-President
Joseph M. Foley, Secretary
Charles Van Buskirk, Treasurer

MAY 1959

ANA To Hold Its Eighty-fourth The American Neurological Association will hold its 84th annual meeting at the Claridge Hotel, Atlantic City, New Jersey, June 15-17, 1959, under the presidency of Dr. Bernard J. Alpers of Philadelphia.... All communications for information regarding the meeting should be forwarded to the ANA Secretary, Dr. Charles Rupp, 133 South 36th Street, Philadelphia 4.

Fifteen Neurologists Certified in Spring Examinations In its spring examinations, held in New Orleans March 16-17, 1959, fifteen physicians were certified in neurology. The new diplomates are C. F. Barlow, Chicago; R. L. Crouch, Chicago; R. D. Currier, Ann Arbor; R. F. Hood, Springfield, Ohio; L. W. Jarcho, Boston; Francis Kruse, Jr., Washington, D. C.; Simeon Locke, Boston; C. H. Markham, Los Angeles; H. H. Schwamb, New York; J. M. Segarra, Boston; I. N. Silberman, San Francisco; C. G. Suter, Rochester, Minn.; B. L. Truscott, New York; L. L. Uzman, Boston; and Henry de Forest Webster, Boston....Owing to the growing number of applications, the Board will give three examinations in 1959: Chicago (October 19-20); New York (December 14-15); and San Francisco (March 14-15)....All inquiries concerning policies and practices of the Board should be sent to Dr. David A. Boyd, Jr., Secretary-Treasurer, Mayo Clinic, 102-110 Second Avenue, S. W., Rochester, Minn.

German To Be Honored Guest at Neurosurgical Meeting The honored guest at the 1959 meeting of the Congress of Neurological Surgeons in the Americana Hotel, Miami, October 28-31, will be William German, distinguished neurosurgeon of Yale University. The primary program item of the meeting concerns discussions of the multiple aspects of brain tumors. The sessions will begin October 28 with a half-day postgraduate course in neuropathology by Louise Eisenhardt....Inquiries should be sent to Dr. Richard L. DeSaussure, Secretary-Treasurer, 20 South Dudley Street, Memphis, Tenn.

English Neurologist Terminates United States Tour Peripatetic Sir Francis Walshe, distinguished physician in neurologic medicine, colorful teacher and adept speaker, is ending his recent visit to this country. At the University of Washington he gave the Bishop Lecture. At the

University of California, San Francisco, he participated in a University Extension Division course devoted to "Neurology of the Cerebral Cortex and Its Related Structures." Here he also addressed the San Francisco Neurological Society on "Mind in Relation to the Brain." He has participated in the ceremonies at the Johns Hopkins School of Medicine in honor of the retirement of Frank Ford and lectured and made rounds at the National Institute of Neurological Diseases and Blindness. His final contribution is his participation in the ceremonies celebrating the fiftieth anniversary of the New York Neurological Institute.

Cerebral Palsy Group To Meet in Los Angeles Glidden L. Brooks, Secretary of the American Academy for Cerebral Palsy, announces that the 13th Annual Meeting will be held in the Statler Hilton Hotel, Los Angeles (November 30-December 2, 1959). Those wishing to participate in the scientific sessions should send a 300 word abstract by May 15 to Albert B. Ferguson, Jr., 125 DeSoto Street, Pittsburgh 13. Those wishing to present films in the audiovisual section should submit their films by June 15 to Dr. Randolph Batson, Vanderbilt University, Nashville 5, Tenn. Members wishing to present scientific exhibits should write the chairman of the Scientific Exhibits Committee, Dr. Einer Johnson, Mayo Clinic, 200 First Street, S. W., Rochester, Minn.... Margaret Jones (Los Angeles) urges members to come early to enjoy Disneyland, Marineland, and other Los Angeles attractions.

Clinical Course in Cerebral Palsy Under the auspices of the Cook County Graduate School of Medicine, Meyer Perlstein will give (June 15-26) his perennial course on cerebral palsy, with special reference to neuromuscular diseases of children. The course, which includes visits to demonstration clinics, is open to physicians interested in the care and treatment of children with neuromuscular disabilities. Registration is limited; the fee for the course is $250....Further information may be obtained from John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 S. Wood Street, Chicago.

Lectures in Child Neurology To Be Given in Virginia The Lynchburg Training School and Hospital of Colony, Va., announces the continuation of a lecture series with patient demonstrations in child neurology and child psychiatry to be given at that institution from May through November 1959. This program was inaugurated last January by Benedict Nagler, Superintendent of the Training School and Hospital....Among the neurologic lecturers are Walter O. Klingman (August 13-15), who will speak on nervous system genetics, postencephalitic residuals, cerebral palsy, and the behavior of children suffering from cerebral impairment; Sidney Carter (October 29-31), who will discuss

seizures, acute cerebellar ataxia, and polyneuritis in children; and Paul M. Ellwood (November 19-21), who will lecture on early diagnosis of neurologic disorders in infancy, muscle weakness in early childhood, and the effects of disturbances of fluids and electrolytes....Further information may be obtained from Dr. Benedict Nagler, Superintendent, Lynchburg Training School and Hospital, Colony, Va.

AAN Members Meet in Los Angeles About 700 members convened at the Statler Hilton Hotel, Los Angeles (April 13-18) for the eleventh annual meeting of the American Academy of Neurology, under the presidency of Francis M. Forster. The scientific sessions were preceded by the presentation of ten special review courses under the acting direction of Maynard M. Cohen, pinch-hitting for A. B. Baker, now in Oslo on a Fulbright scholarship. The AAN sessions were followed by the Second International Symposium on Myasthenia Gravis (April 18-19), Kermit E. Osserman chairing the myasthenia program which was co-sponsored by the Myasthenia Gravis Foundation and the National Institute of Neurological Diseases and Blindness....The AAN program provided 86 scientific papers; 33 scientific exhibits; 5 scientific demonstrations and movies; 4 voluntary society exhibits (Illinois Epilepsy League, Muscular Dystrophy Associations of America, Myasthenia Gravis Foundation, and the National Society for Crippled Children and Adults); and 24 technical exhibits....Special sessions were held for the AAN sections of neuroanatomical sciences, neurochemistry, and neuropharmacology which met jointly. The program of the newly created section of child neurology was included in the general scientific session (April 16) under Richard L. Masland, chairman, and Philip R. Dodge, secretary....The AAN festive activities began with the Early Bird Cocktail Party on April 15 and culminated with the annual Academy banquet on April 17.

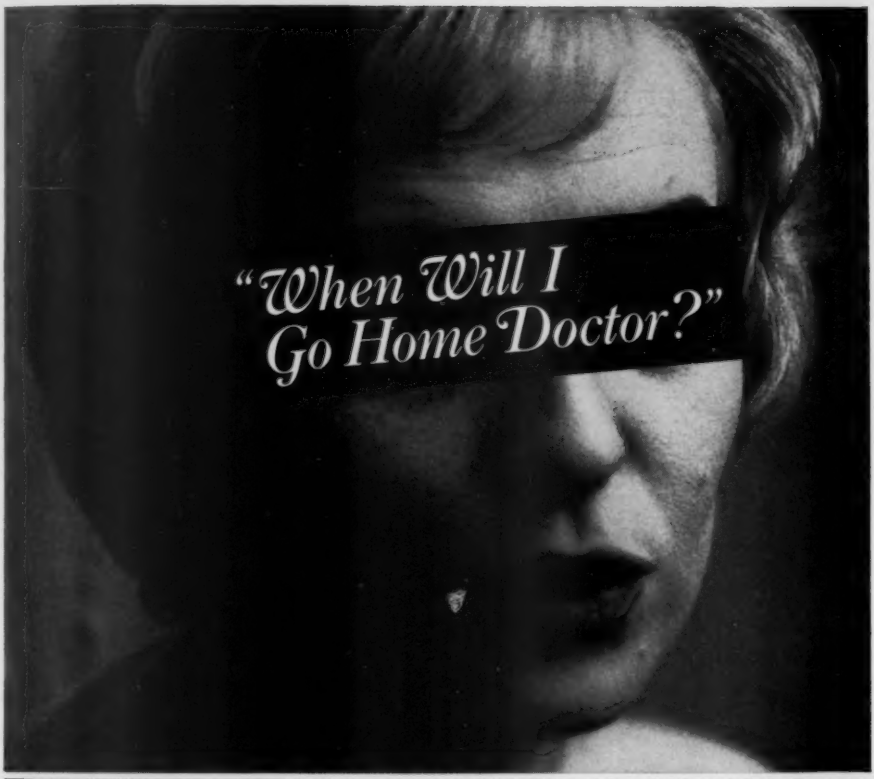
361 Register for Review Courses A total of 361 physicians and scientists registered for the traditionally successful AAN review courses. The highest individual course registration was 143 in the one given by Benjamin Boshes on common neurologic disorders for the general practitioners. The next most popular courses in order named, were: EEG (78), F. Morrell; neurophysiology (77), J. L. O'Leary; neurochemistry (59), D. B. Tower and M. M. Cohen; neuroroentgenology (47), A. L. Sahs; neuropathology (39), E. R. Nelson; special diagnostic procedures (39), N. S. Schlezinger; neuritis and neuralgias (34), C. A. Kane; and neuropharmacology (28), C. C. Pfeiffer....Planned for the 1960 program are new courses in infectious diseases (C. A. Kane); child neurology (P. M. Ellwood); genetics and genetic counseling (L. T. Kurland); neuro-ophthalmology (N. S. Schlezinger); aphasia and

language disorders (J. R. Brown); and the neurologic aspects of internal disease (G. L. Glaser).

Tourtellotte Wins Mitchell Award Wallace W. Tourtellotte, Assistant Professor of Neurology at the University of Michigan, was the 1959 recipient of the S. Weir Mitchell Award. His prize-winning essay on the lipid content of the normal spinal fluid was read at the opening of the general scientific sessions (April 16)....The S. Weir Mitchell Award, made possible by the AAN Women's Auxiliary, provides $200 to be given to the junior member submitting the best essay on a neurologic subject. This year's Weir Mitchell prize committee consisted of Walter O. Klingman, chairman; Arnold P. Friedman; and Adolph L. Sahs.

Rose Assumes AAN Leadership As of noon, Saturday, April 18, Augustus S. Rose, Head of Neurology at U.C.L.A., took up the gavel as the new President of the American Academy of Neurology, succeeding Francis M. Forster. The President-Elect is Adolph L. Sahs of the State University of Iowa. Elected by unanimous acclaim were Joseph M. Foley (Boston), Vice-Preident; Robert Utterback (Memphis), Secretary; and Charles M. Poser (Kansas City), Treasurer....The newly elected AAN Trustees are Benedict Nagler (Lynchburg) and Sidney Carter (New York)....Further details on this meeting will be forthcoming in the June Newsletter....The 1960 annual meeting of the Academy will be held at the Eden Roc Hotel, Miami Beach, Fla. (April 21-26).

Reese Bailey



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1. Goldman, D.: Am. J. M. Sc. 235:67 (Jan.) 1958. 2. Morehouse, W. G., and Freed, J. E.: Monographs on Therapy 3:32 (May) 1958. 3. Leger, V.: Union Med. Canada 87:831 (July) 1958. 4. Bruckman, N. S.; Saunders, J. C., and Kline, N. S.: Monographs on Therapy 3:24 (May) 1958.

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1. Mitchell, E.H.: M. Ann. District of Columbia *27*:190 (April) 1958. 2. Cooper, C.D., and Epstein, J.H.: Am. J. M. Sc. *235*:448 (April) 1958. 3. Vazuka, F.A.: Neurology *8*:446 (June) 1958. 4. Cobey, M.C.: Am. Surgeon *24*:358 (April) 1958. 5, 6. Wein, A.B.: M. Ann. District of Columbia *27*:346 (July) 1958; Clin. Med. *6*:44 (Jan.) 1959.

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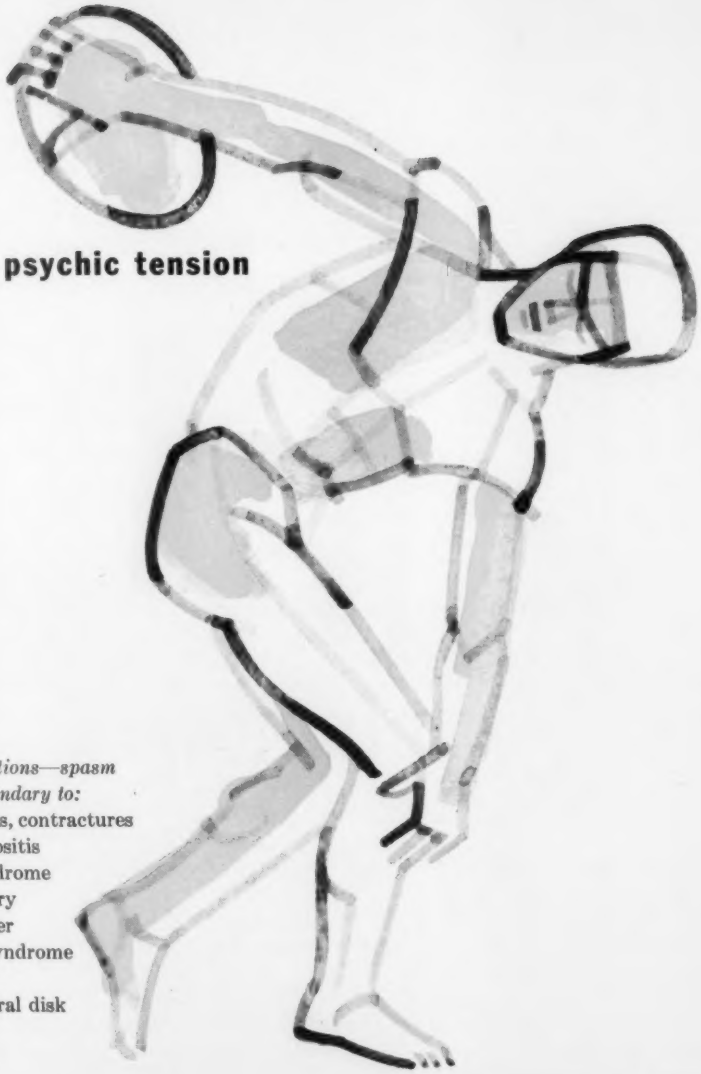

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whiplash injury
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References: 1. Barsa, J. A.: Am. J. Psychiat. 115:79, July 1958. 2. Graffagnino, P. N., Friel, P. B. and Zeller, W. W.: Connecticut M. J. 21:1047, Dec. 1957. 3. Hollister, L. E., Elkins, H., Hiler, E. G. and St. Pierre, R.: Ann. New York Acad. Sc. 67:789, May 9, 1957. 4. Pennington, V. M.: Am. J. Psychiat. 114:257, Sept. 1957. 5. Tucker, K. and Wilensky, H.: Am. J. Psychiat. 113:698, Feb. 1957.

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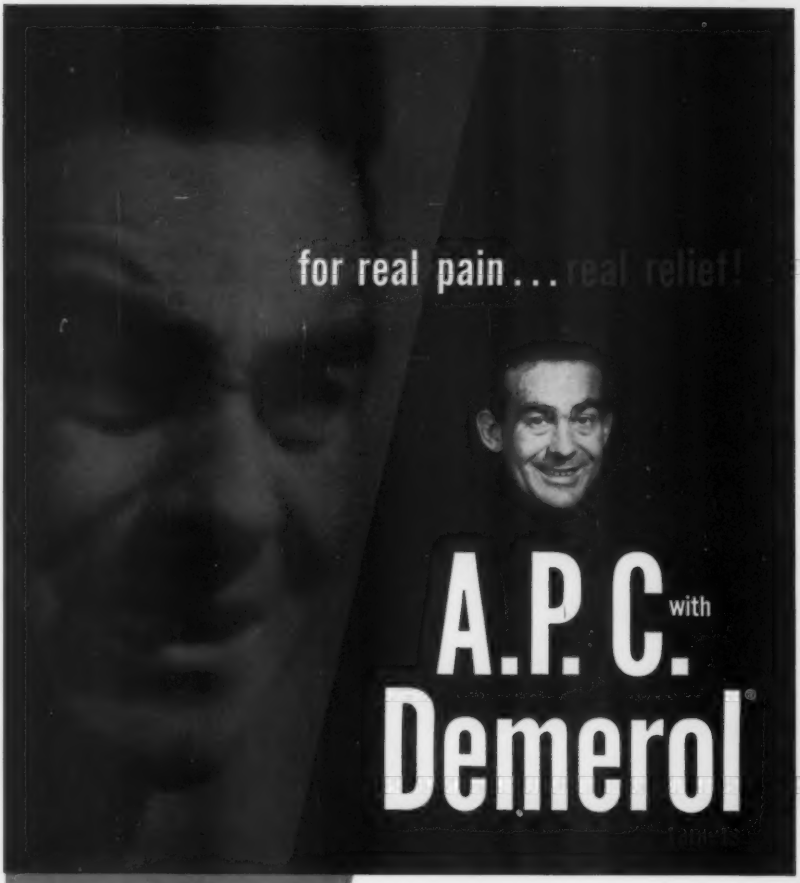

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